STUDIES IN ASYMMETRIC SYNTHESIS USING CHIRAL ACETALS AND DEVELOPMENT OF NEW SYNTHETIC METHODS FOR ORGANIC SYNTHESIS

A Thesis Submitted
in Partial fulfilment of the Requirements
for the degree of
DOCTOR OF PHILOSOPHY

by
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to the
DEPARTMENT OF CHEMISTRY

INDIAN INSTITUTE OF TECHNOLOGY KANPUR

NOVEMBER, 1995

DEDICATED

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STATEMENT

I hereby declare that the matter embodied in this thesis entitled "Studies in Asymmetric Synthesis using Chiral Acetals and Development of New Synthetic Methods for Organic Synthesis" is the result of investigations carried out by me in the Department of Chemistry at Indian Institute of Technology (I.I.T.) Kanpur, India under the supervision of Prof. Y.D. Vankar.

In keeping with the general practice of reporting scientific observations, due acknowledgement has been made whereever the work described is based on the findings of other investigators.

M. V. Ram Redd

I.I.T. Kanpur
November, 1995

M. Venkat Ram Redd

DEPARTMENT OF CHEMISTRY

INDIAN INSTITUTE OF TECHNOLOGY KANPUR, INDIA

CERTIFICATE I

This is to certify that Mr. M. Venkat Ram Reddy has satisfactorily completed all the courses required for the Ph.D. programme at our department. These courses include

CHM 602	ADVANCED ORGANIC CHEMISTRY
CHM 605	PRINCIPLES OF ORGANIC CHEMISTRY
CHM 611	PHYSICAL ORGANIC CHEMISTRY
CHM 624	MODERN PHYSICAL METHODS IN CHEMISTRY
CHM 625	PRINCIPLES OF PHYSICAL CHEMISTRY
CHM 645	PRINCIPLES OF INORGANIC CHEMISTRY
CHM 800	SPECIAL SEMINAR
CHM 801	GENERAL SEMINAR
CHM 900	Ph.D. THESIS

Mr. M. Venkat Ram Reddy has successfully completed the written and oral qualifying examinations in September, 1991. He delivered his "STATE OF ART" seminar in October, 1991.

Prof. P. Gupta Bhaiya
Convener
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Prof. P. K. Ghosh
Professor and Head
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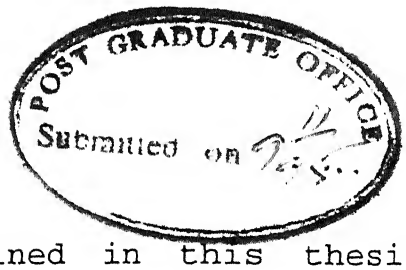
November, 1995



CERTIFICATE II

It is certified that the work contained in this thesis entitled "Studies in Asymmetric Synthesis using Chiral Acetals and Development of New Synthetic Methods for Organic Synthesis" has been carried out by Mr. M. Venkat Ram Reddy, under my supervision and the same has not been submitted elsewhere for a degree.

Dr. Y.D. Vankar
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Department of Chemistry
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November, 1995

ABSTRACT

The thesis entitled "Studies in Asymmetric Synthesis using Chiral Acetals and Development of New Synthetic Methods for Organic Synthesis" has been divided into two chapters. Chapter I which deals entirely with chiral acetals is subdivided into two parts. Chapter II contains four new synthetic methods based on newer reagent system.

CHAPTER I

PART A : REGIOSELECTIVE SYNTHESIS OF ACHIRAL AND CHIRAL 3-KETO ACETALS AND CHIRAL 2-KETO ACETALS AND THEIR REACTIONS

When 2,3-olefinic acetals are subjected to bromohydrin formation the reaction takes place regioselectively to give 2-bromo-3-hydroxy acetals. This has been utilised in the regioselective synthesis of achiral and chiral 3-keto acetals and chiral 2-keto acetals. Further, achiral 3-keto acetals have been hydrolysed to obtain 1,3-dicarbonyl compounds which are useful synthetic intermediates. Chiral 2-keto acetals and 3-keto acetals have been subjected to $LiAlH_4$ reduction and MeMgI addition to see the effect of chiral acetal on these reactions. 2-Keto acetals have been found to provide high level of asymmetric induction whereas 3-keto acetals provide moderate selectivity due to proximity difference and conformational rigidity.

PART B : EFFECT OF CHIRAL ACETALS ON RADICAL REACTIONS AND SYNTHESIS OF α-METHYLENE-γ-BUTYROLACTONES

Four chiral 2,3-olefinic acetals (two cyclic and two acyclic from two chiral diols which are in turn prepared from R,R-tartaric

acid) have been bromopropargylated with N-bromosuccinimide and propargyl alcohol. Cyclisation using n-tributyltinhydride followed by chromium trioxide oxidation has furnished four α-methylene-γ-butyrolactones. Intermolecular C-C bond formation reactions involving radical reactions have also been studied to see the effects of chiral acetals on these reactions. In both intramolecular as well as intermolecular cases, the diastereoselectivity has been found to be low.

CHAPTER II

PART A : ONE POT SYNTHESIS OF NITROACETAMIDES FROM OLEFINS WITH CERIC AMMONIUM NITRATE-SODIUM NITRITE-ACETONITRILE REAGENT SYSTEM

Conversion of olefins to nitroacetamides has been achieved conveniently in moderate to good yields. In place of acetonitrile when acrylonitrile or benzonitrile was used the corresponding nitroamides were formed. Initial formation of a nitro radical which adds on to the olefin to give a carbon radical, which then gets oxidised to a carbonium ion followed by attack of acetonitrile in Ritter fashion gives the nitroacetamides. In cases where carbonium ion is well stabilised and the proton to be extracted is very acidic nitroolefins are formed.

PART B : ONE STEP SYNTHESIS OF α-NITROKETONES FROM OLEFINS WITH TRIMETHYLSILYLNITRATE-CHROMIUM TRIOXIDE REAGENT SYSTEM

Olefins when treated with the above reagent system give α-nitroketones in good yield. This reagent system is applied to cyclic, acyclic and phenyl substituted olefins which highlights its generality. Addition takes place in Markownikoff fashion in cases where unsymmetrical olefins are used. Mechanism and scope

of the reagent system is also mentioned in this chapter.

PART C : ONE STEP SYNTHESIS OF α-AZIDOKETONES FROM OLEFINS WITH TRIMETHYLSILYLAZIDE-CHROMIUM TRIOXIDE REAGENT SYSTEM

Olefins when treated with this reagent system are converted into α-azidoketones in moderate to good yields. Cyclic, acyclic and phenyl substituted olefins have been found to react with this reagent system with ease to give the corresponding α-azidoketone. This method has advantages over the existing methods in terms of simple reaction conditions and cheaply available starting materials.

PART D : H-ZSM-5 CATALYSED REGIOSELECTIVE ISOMERISATION OF GLYCIDIC ESTERS TO α-HYDROXY-β,γ-UNSATURATED ESTERS

H-ZSM-5 conveniently isomerises a wide range of glycidic esters to the corresponding α-hydroxy-β,γ-unsaturated esters in good yields. Not even a trace amount of keto ester was formed during the isomerisation of any glycidic ester. This suggests that the transition state shape selectivity of the catalyst plays an important role during the course of these reactions. Because of the advantages associated with the use of zeolites, this method is industrially useful too.

ACKNOWLEDGEMENTS

I wish to take this opportunity to express my deep sense of gratitude and sincere thanks to my thesis supervisor Prof. Y.D. Vankar for his competence guidance, continuous encouragement and personal involvement during the course of my research work at IIT Kanpur. Words will not be adequate to quantify his immense patience, tolerance and understanding. His *Never Say Die* attitude has always helped me in doing the things successfully. His stimulating discussions have helped me in improving my chemistry. Indeed I got very good training under his guidance.

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My special thanks are due to Dr. K.P. Madhusudanan and Dr. Raja Roy of CDRI, Lucknow, for mass spectral and high resolution proton NMR analyses.

It was an extremely enjoyable experience for me working with my lab colleagues Dr. Padma S. Vankar (Padmadi), Dr. Kavita Shah, Dr. Indrani Bhattacharya, Sangeeta, Kumar, Anuradha, Shatrughan and Bharat. Their whole hearted cooperation and congenial company has always eased my going in this research group. I sincerely thank all of them.

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Sincere thanks are due to Kamal and Sushil for the wornderful company they have always been throughout my stay here. Their company has converted the dull moments into cheerful moments.

The caring attitude of friends Dr. Damodar Reddy, Dr. M. Ravikant, Dr. Madhav Reddy, Prabhucharan (PC), Govind (Vicas), Sunder (beast), Nachiketa (Tomy), Joginder (Liffo), Jeyaraj, Dastagiri, Dr. Debnath, Arpita, Behra, Maiti, Balvinder Singh, Simant, Ashish, Sonu and others whose names have not been mentioned here cannot be forgotten.

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I specially thank Sangeeta for proof-reading the entire manuscript patiently. Her patience, love and affection has always kept me in a positive frame of mind.

My family has contributed much to this thesis both tangible and intangible, visible and invisible. My parents have tolerated and provided much over the years, including love and support. My sisters, brother and brother-in-laws *have always been there* throughout with me when I needed their help and support.

CHAPTER I

PART A

REGIOSELECTIVE SYNTHESIS OF ACHIRAL AND CHIRAL 3-KETO ACETALS AND CHIRAL 2-KETO ACETALS AND THEIR REACTIONS

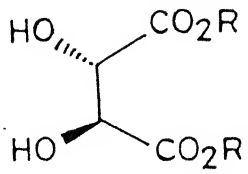
I.A.1 INTRODUCTION

Upon first inspection, it might appear that the introduction of a symmetry element within a chiral auxiliary would be antithetical to the stated objective of achieving asymmetric induction in a chemical transformation. In fact, the enantioface differentiation to provide asymmetric induction requires that the auxiliary has mirror inversion symmetry and therefore, need not be asymmetric, must be dissymmetric. In majority of the cases for absolute stereocontrol, the presence of a C_2 symmetry axis within the chiral auxiliary serves very important function of dramatically reducing the number of possible competing diastereomeric transition states. It is almost universally observed that auxiliaries with C_2 symmetry elements perform in their capacity as stereochemical directors to provide higher levels of absolute stereochemical control as compared to those totally lacking in symmetry.[1]

Out of all C_2 symmetric chiral auxiliaries, chiral acetals have special importance in asymmetric induction. The usefulness of these auxiliaries in asymmetric synthesis is evident from the literature.[2] Some of the most commonly encountered diols used in preparing chiral acetals are shown in Figure 1.

A literature survey pertaining to the utility of chiral acetals in organic synthesis is briefly delineated in the following few pages.

Pioneering in the field of chiral acetals, W.W. Johnson's group[3] used an acetal of R, R-2,3-butane diol in their cationic biomimetic cyclisations (Scheme 1). Of the four stereoisomers



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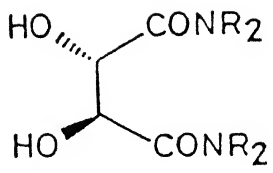

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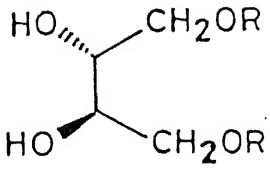

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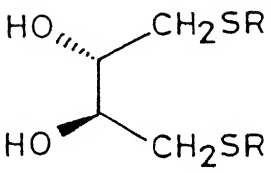

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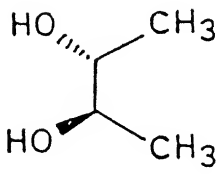

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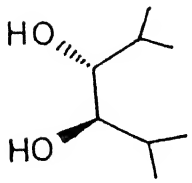

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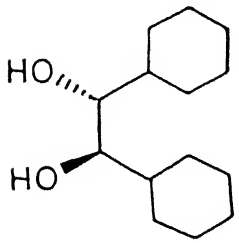

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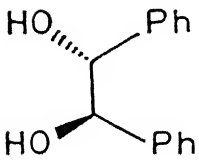

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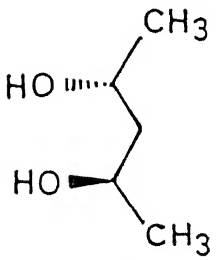

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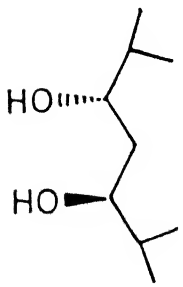

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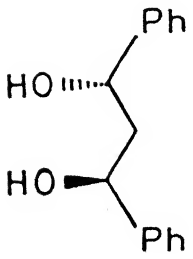

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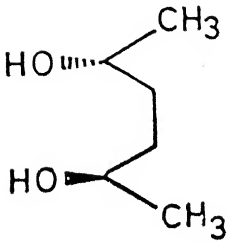

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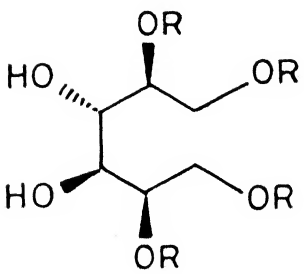
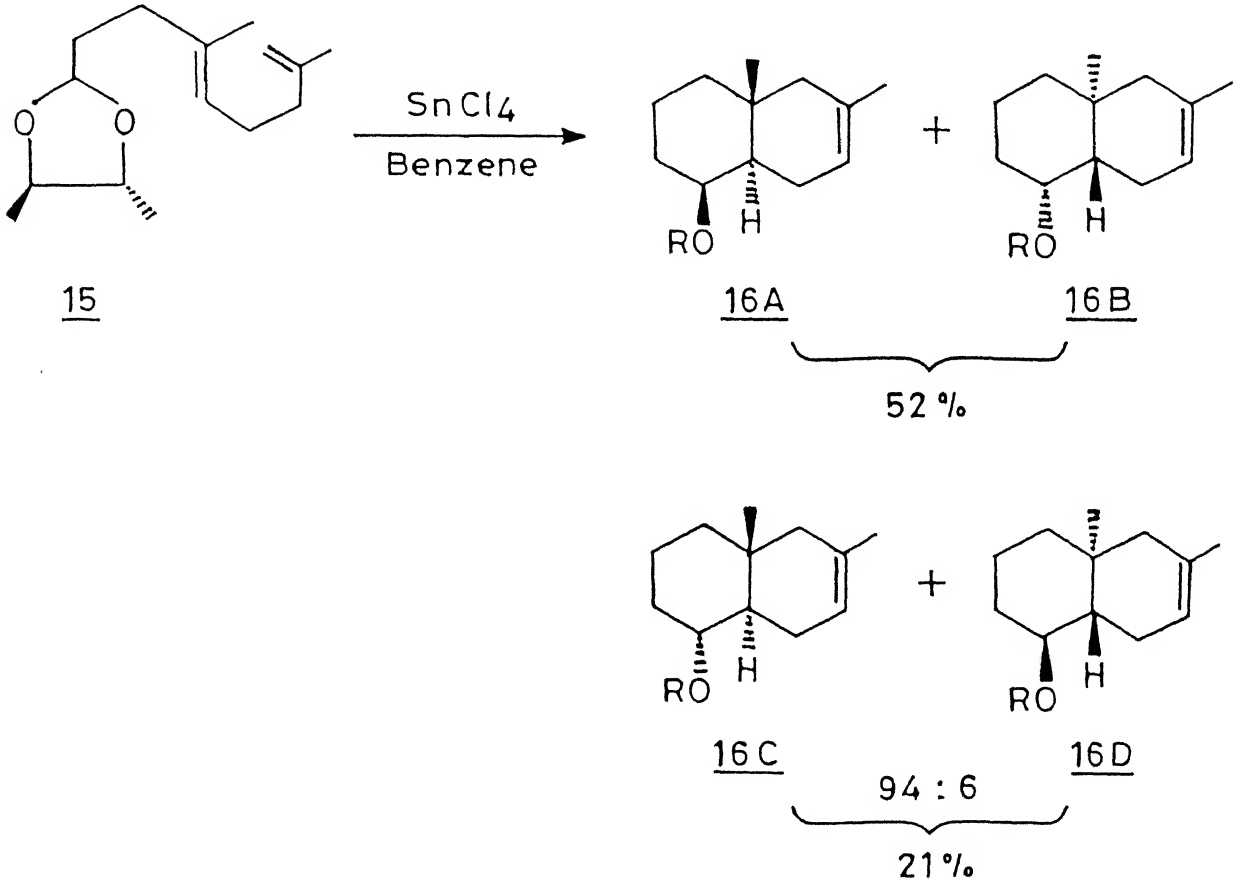


(13)

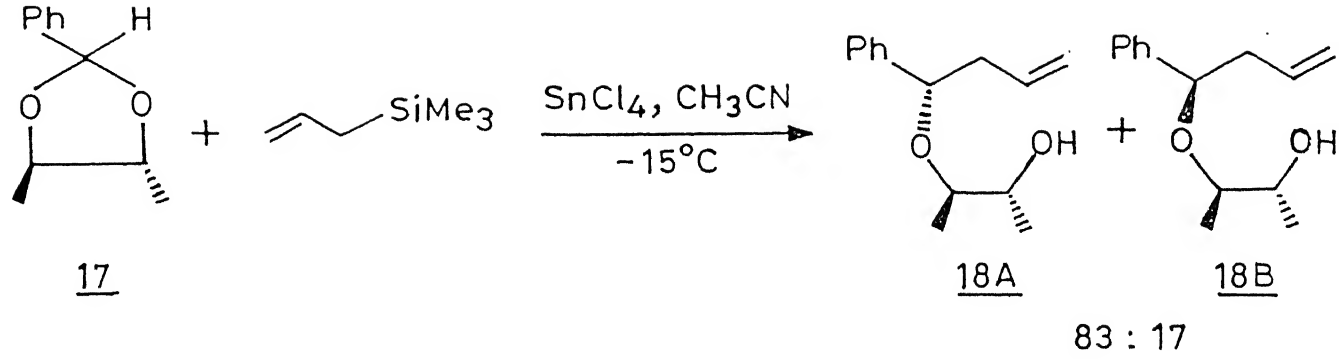
obtained in this $SnCl_4$ catalysed reaction, two major ones B and C have the same absolute configuration at the acetal carbon. This represents a very high degree of diastereoselectivity in the reaction process (d/e 86%).



SCHEME - 1

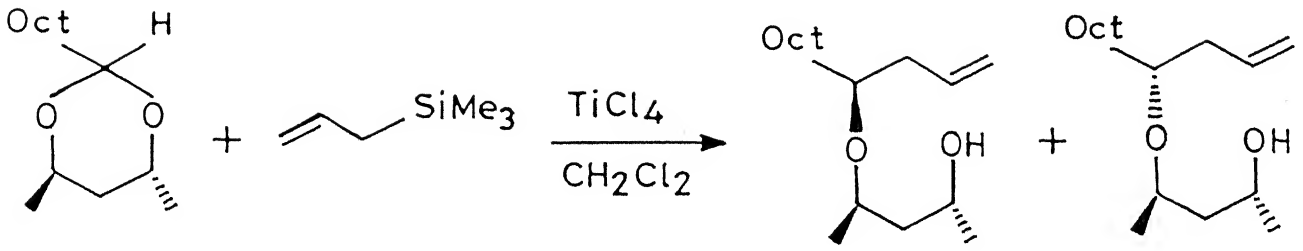
Johnson et al have also found[4] that the cleavage of the acetals is highly diastereoselective with milder Lewis acid, viz. a combination of $TiCl_4$ and $Ti(O^iPr)_4$ (Scheme 2).

α, β-Ethylenic acetals have a dual reactivity. They may be cleaved by direct nucleophilic attack (SN^2) or by attack at the γ position, with allylic rearrangement (SN^1). For example, the



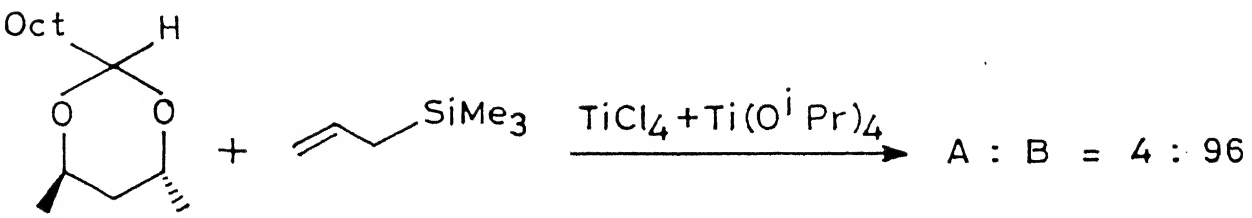
17 18A 18B

83 : 17



19 20B 20A

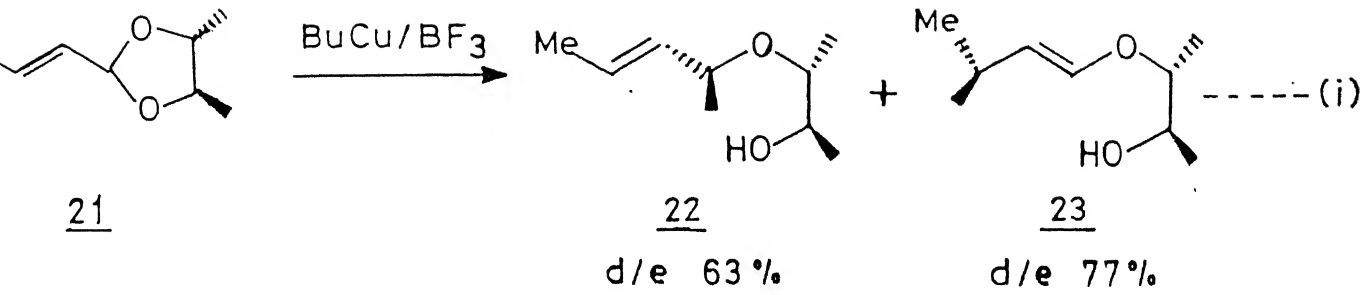
A : B = 12 : 88



A : B = 4 : 96

SCHEME - 2

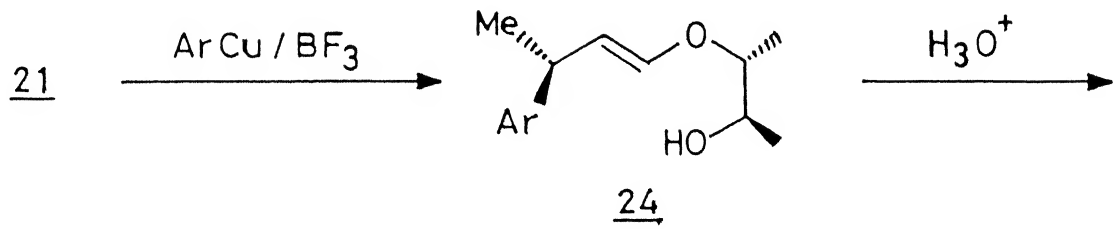
reaction of crotonaldehyde acetal (21) and $BuCu/BF_3$, representative of alkyl copper reagents, is not regioselective, although diastereoselective (Scheme 3). On the other hand, aryl[5] and alkenyl[6] copper reagents are completely regioselective and highly diastereoselective. The degree of diastereoselectivity is increased when aryl or vinyl copper reagents are used (equations (ii) and (iii), Scheme 3).



21 22 23

d/e 63 % d/e 77 %

Product Ratio : 57/43



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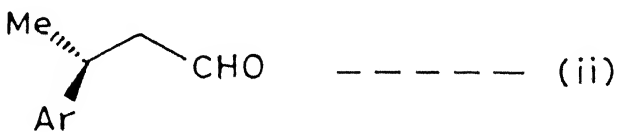
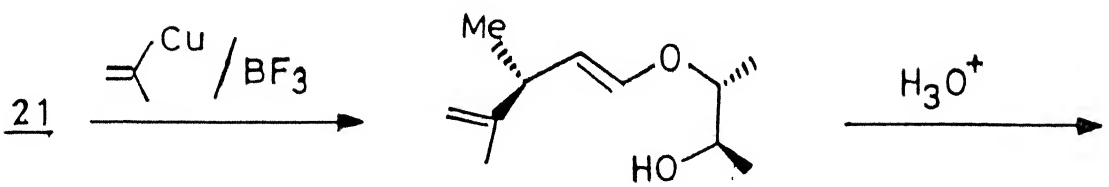


25

e/e 95%



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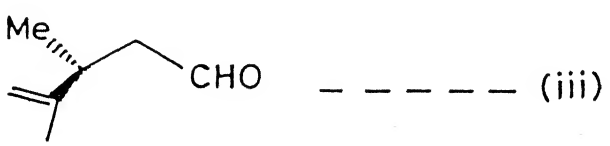
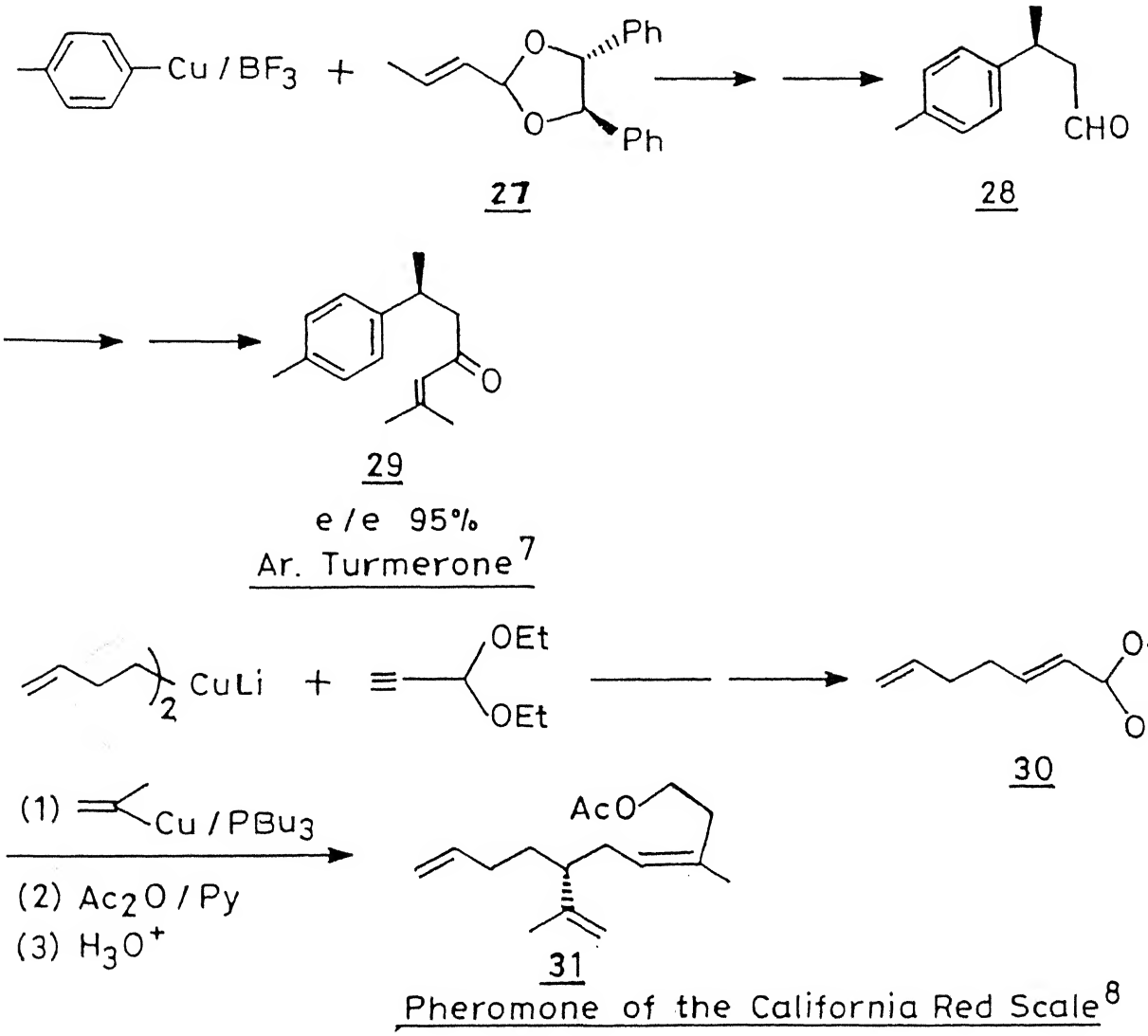


27

e/e 85%

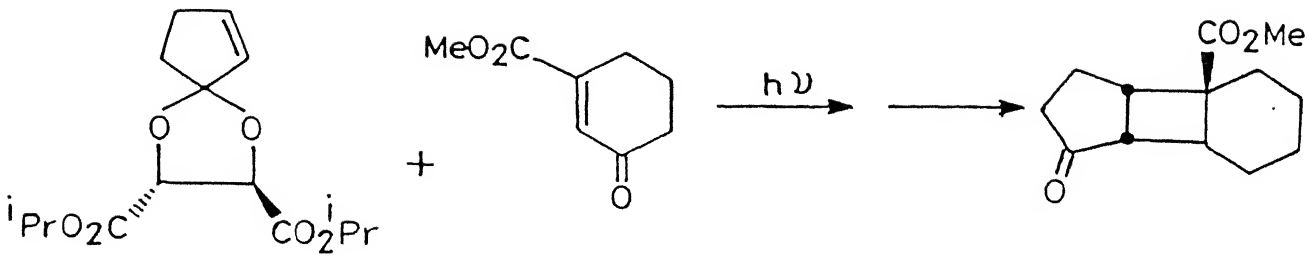
SCHEME - 3

These reactions have been applied in the synthesis of some natural products, eg. Ar. Turmerone 29 and a pheromone of the California Red Scale 31 (Scheme 4).



SCHEME-4

High diastereoselectivity has been attained in photochemical (2+2) additions employing an α,β-ethylenic acetal[9] 32, the best auxiliary being diisopropyl tartrate (Scheme 5).

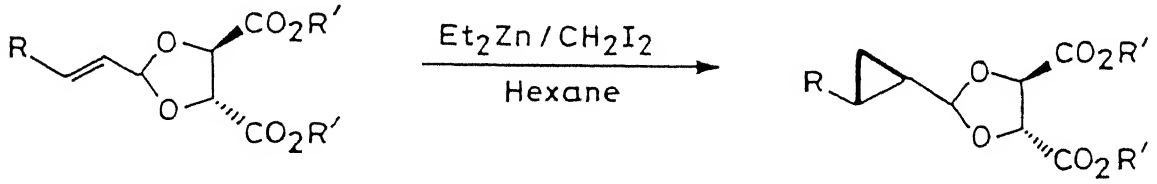


32 33 34

e/e 84%

SCHEME -5

Yamamoto et al[10] have described a highly diastereoselective asymmetric Simmons-Smith reaction on various acetals of enals and applied it to the synthesis of (5R), (6R)-5, 6-methanoleukotriene A_4[11] 40 (Scheme 6).



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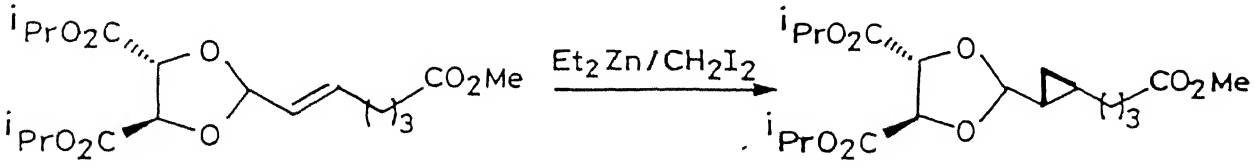
e/e 88 - 94%



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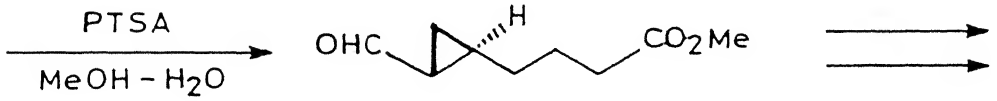

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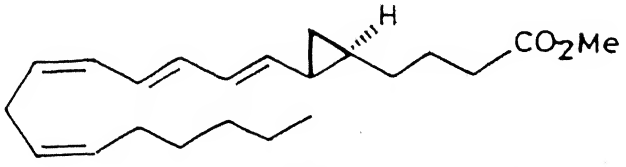
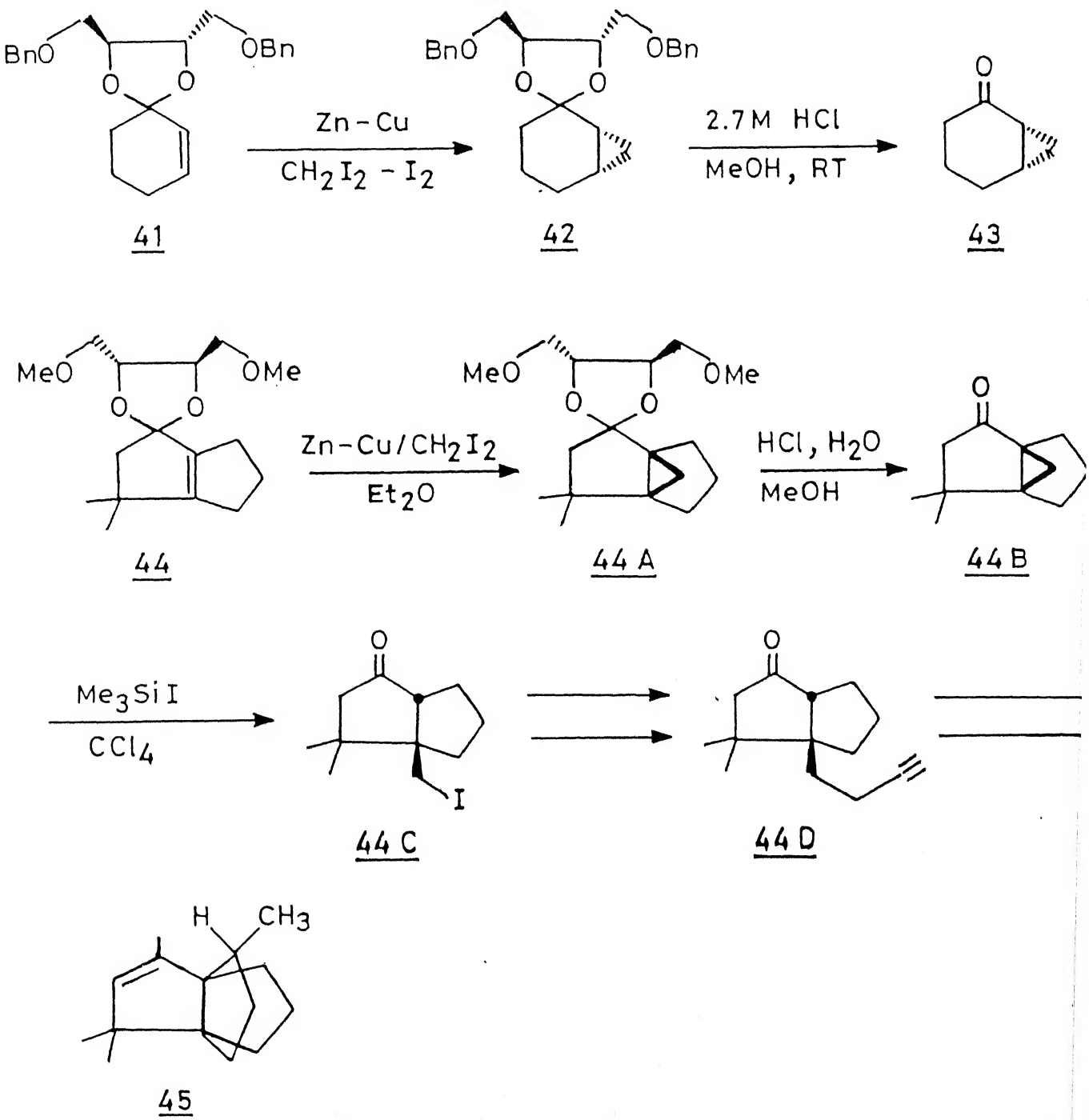


40

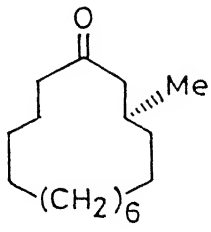
5, 6 - Methanoleukotriene A_4

At the same time, Mash et al have utilised cyclic 2,3-olefinic acetals for highly enantioselective cyclopropanations[12] and applied this methodology in the synthesis of (+) Modhephene[13] 45 (Scheme 7).



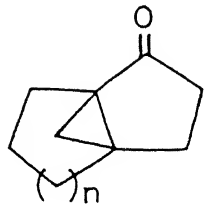
SCHEME -7

Some of the other natural products which have been synthesised by this method are shown in Figure 2.



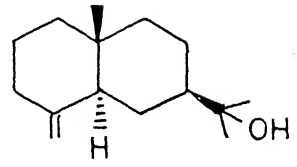
46

(R) - Muscone[14]



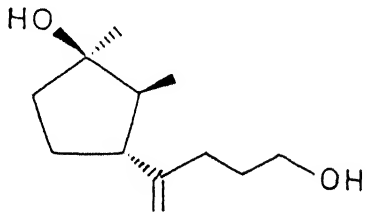
47

Propellanones[15]



48

(+) - β - Sudesmol[16]

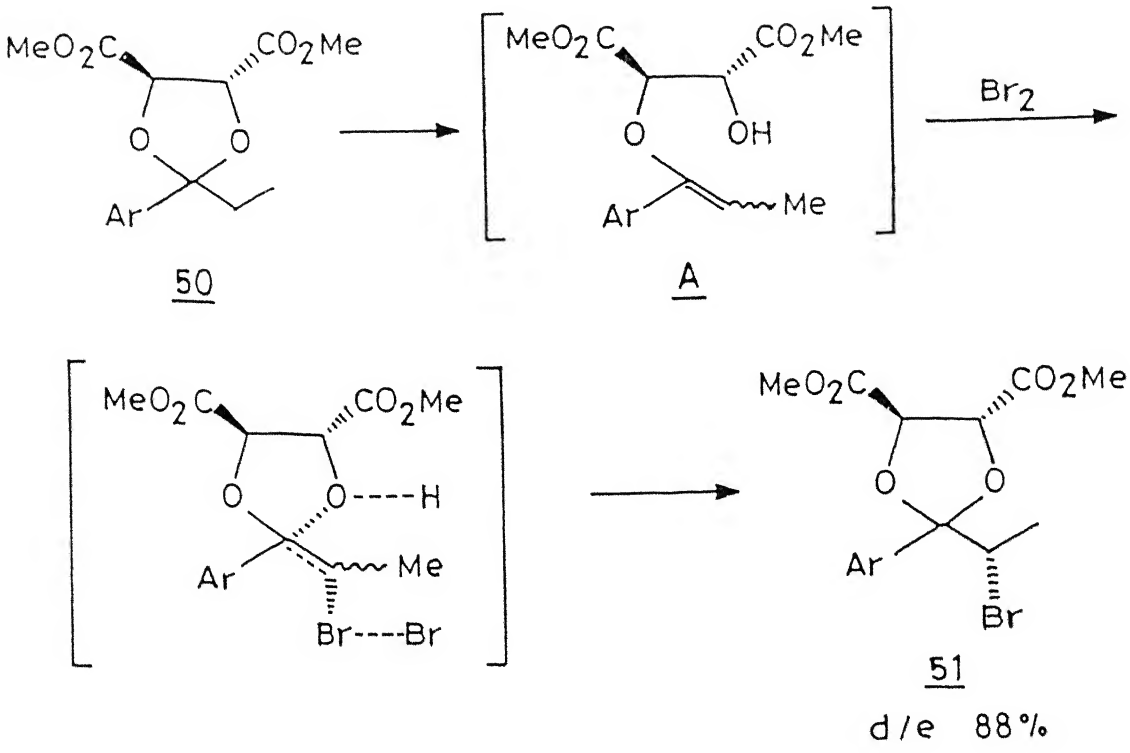


49

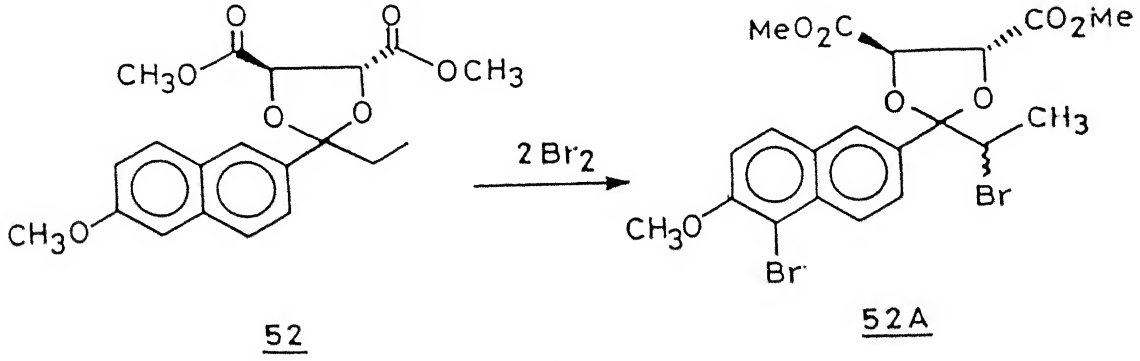
(−) - Chokol A[17]

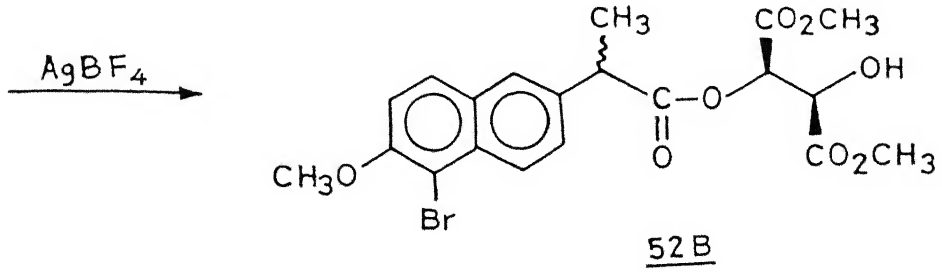
FIGURE 2

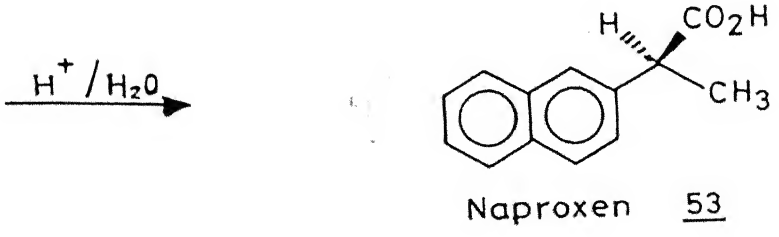
Bromination of the chiral acetal of an aryl alkyl ketone affords the α-bromoacetal with high diastereoselection[18]. The reaction is believed to proceed through an enol ether 'A' (Scheme 8). Careful hydrolysis of ketal furnishes an optically active α-bromoketone[19] 51 which serves as a useful intermediate for the synthesis of chiral 2-alkyl-2-aryl acetic acids[20] such as S(+)-Naproxen 53 and S(+)-Ibuprofen[21] 54 (Scheme 9). This synthesis has been scaled upto an industrial process by the Zambon group. Thus, Naproxen is one of the very few examples in the world of a large scale asymmetric synthesis.



SCHEME - 8

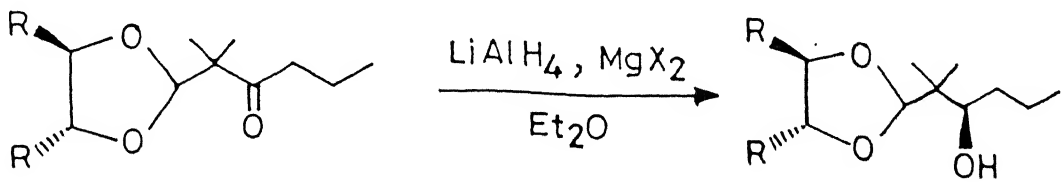




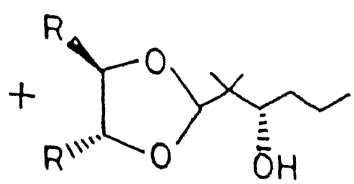


SCHEME - 9

Lithium aluminium hydride reduction of a ketone β to a non-functionalized chiral dioxolane ring 55 affords one major diastereomeric alcohol (d/e 66%). However, addition of $MgBr_2$ gives the epimeric alcohol (d/e 82%)[22]. Changing to a dioxolane having chelating heteroatoms on the ring improves the d/e to 98%. In this case, addition of MgX_2 salt does not change the selectivity. This method was applied to a short synthesis of (+)-Pedamide[23] 56 (Scheme 10).

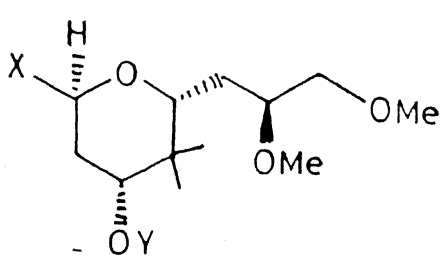


55 55A



55B

R = Me or Ph	$LiAlH_4$	83	:	17
	$LiAlH_4/MgBr_2$	9	:	91
$R = CH_2OMe$	$LiAlH_4$	99	:	1

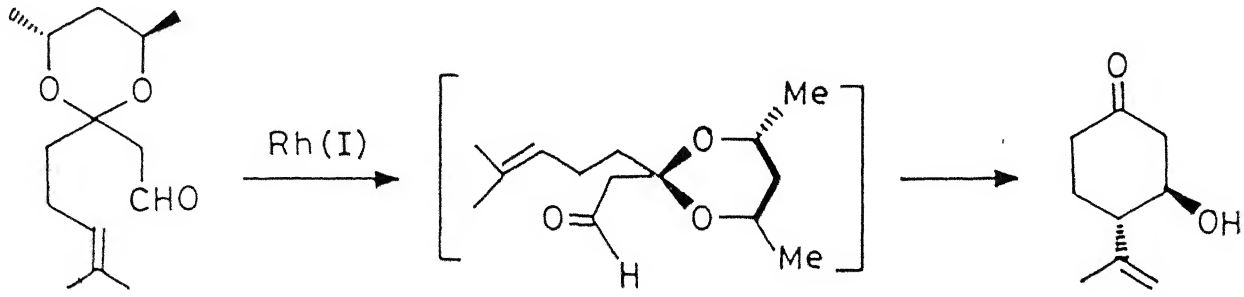


(+) - PEDAMIDE 56

X = $CONH_2$
Y = COPh

SCHEME - 10

Rh(I) catalysed intramolecular cyclisation of a chiral acetal affords a single diastereomer. A conformationally rigid dioxolane ring, arising from 2,4-pentanediol serves to maintain a tight transition state throughout the whole process[24-26] (Scheme 11).

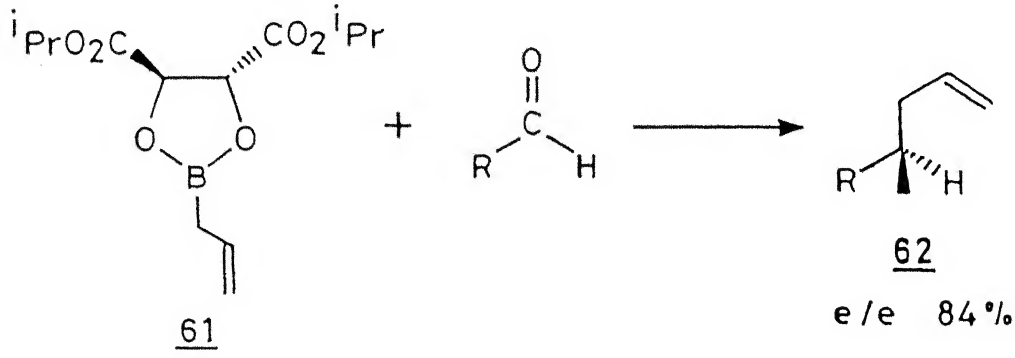


57 58

e/e 99%

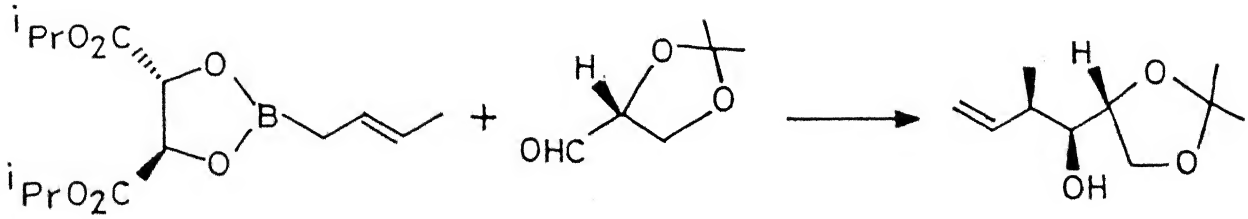
SCHEME - 11

Further contributions in the area of chiral allyl borane reagents have been made by Yamamoto[27], Midland[28], Roush[29,30] and Brown[31] with the results reported by Roush and Brown representing the highest levels of stereochemical control in alkylation reactions (Scheme 12).



61 62

e/e 84%



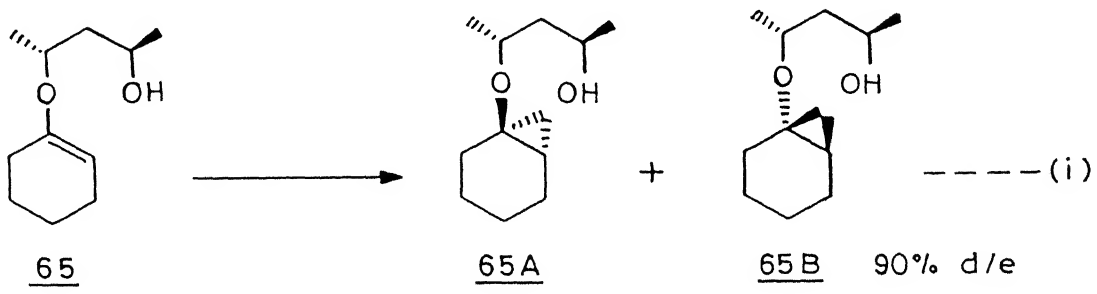
63 64

e/e 81%

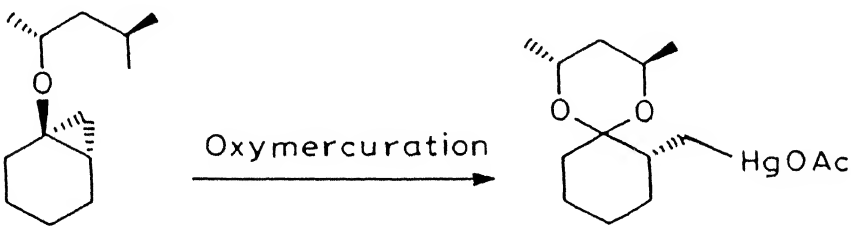
SCHEME - 12

Diastereo differentiating Simmon-Smith reaction on enol ethers generated from acetal 65 is achieved by Sugimura et al[32,33] (Equation (i), Scheme 13).

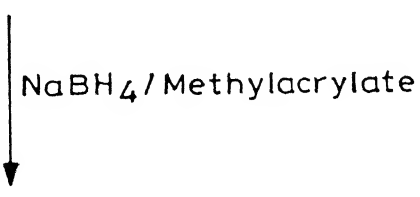
These cyclopropanated compounds are converted into useful synthetic intermediates 67 and 69 (Scheme 13).

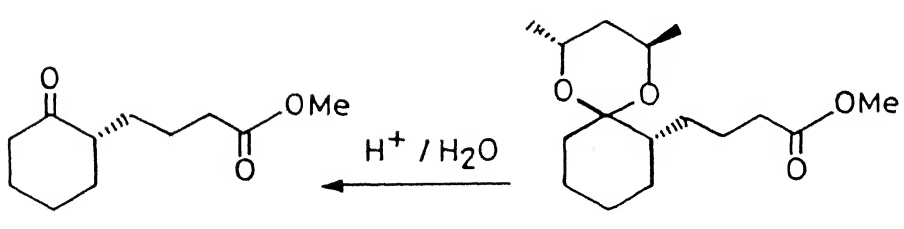


65 65A 65B 90% d/e

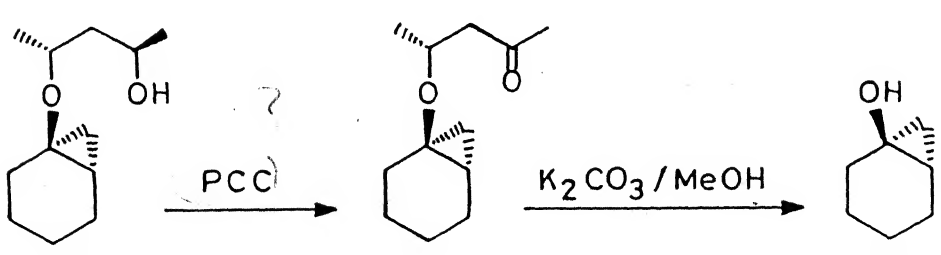


65A 66



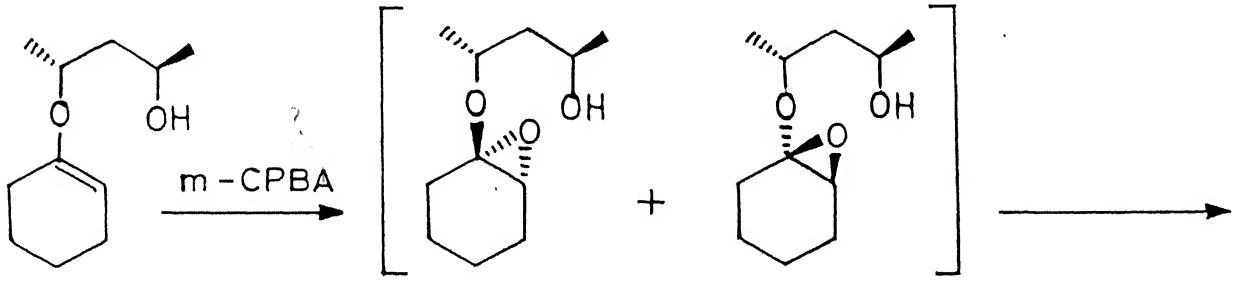


67 66A

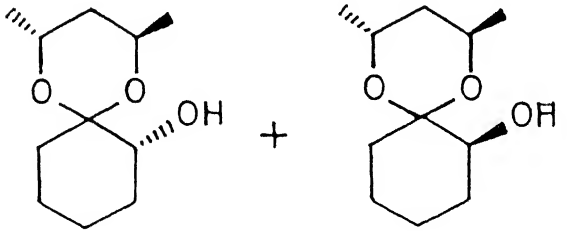


65A 68 69

Diastereoface differentiating oxidations with m-chloroperbenzoic acid have been carried on the chiral enol ether prepared from cyclohexanone and optically active 2,4-pentane diol. It proceeds from -72 to 39°C to give a diastereomeric mixture of the corresponding 2-hydroxy cyclohexanone acetal[34]. The diastereomeric excess of the product is found to reach almost 100% at -72°C (Scheme 14).



65



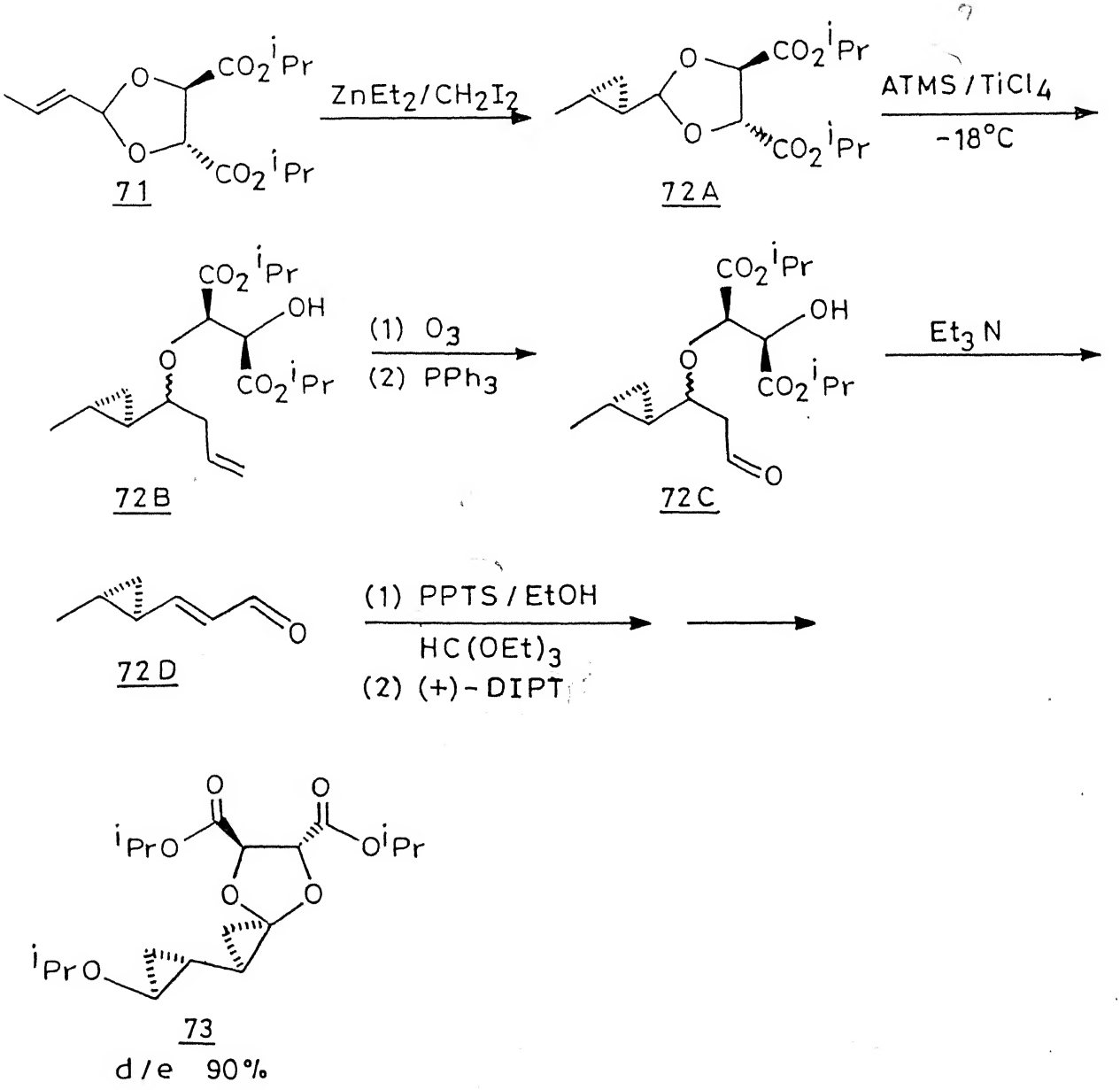
70A + 70B

d/e >99 % at -72°C

SCHEME-14

Very recently an iterative strategy for the synthesis of conjugated cyclopropanes has been developed resulting in the generation of the trans, trans-dicyclopropane derivative in high enantiomeric excess[35]. The diisopropyl tartrate auxiliary is reported to give high selectivity for acyclic unsaturated acetals. Crotonaldehyde acetal gives 94% e/e upon cyclopropanation. Its

reaction with allyltrimethylsilane/$TiCl_4$ at -18°C gives inseparable mixture of diastereomers corresponding to addition to the acetal. The mixture is subjected to ozonolysis to give a very high yield of aldehyde mixture. Treatment with triethylamine followed by acetalization with (+)-DIPT followed by cyclopropanation gives a single isomer (Scheme 15).



71 72A 72B 72C 72D

73

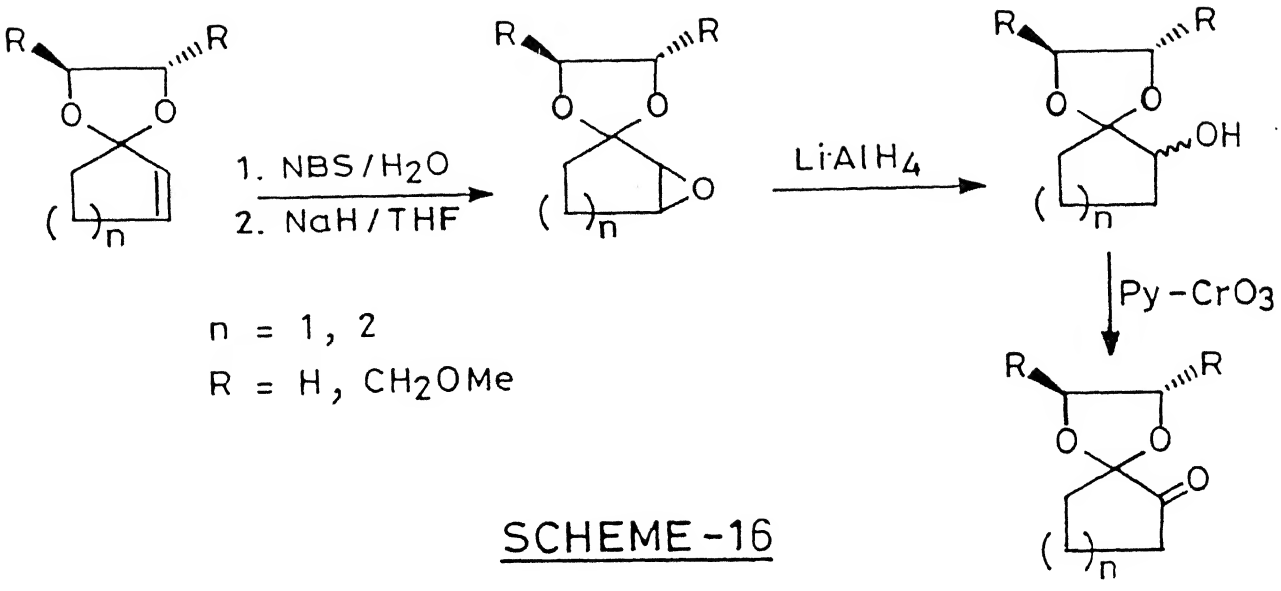
d/e 90%

SCHEME-15

I.A.2 RESULTS AND DISCUSSION

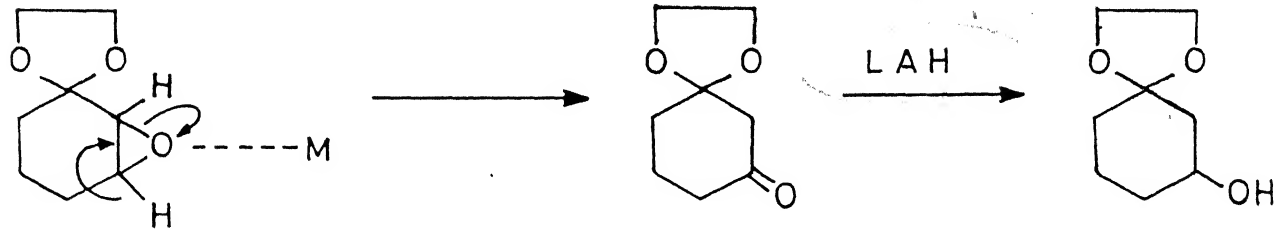
In the introduction part of this chapter, a brief literature survey pertaining to the reactions of chiral acetals has been presented. These reactions have been found to give fairly high degree of diastereo- and enantioselectivities. Recently from our laboratory achiral as well as chiral 2,3-olefinic acetals have been utilised in the preparation of 2-nitro and 3-nitro olefinic acetals regioselectively. These have been further utilised in the synthesis of α-methylene-γ-butyrolactones[36]. Also, achiral 2,3-olefinic acetals have been further utilised in the synthesis of 1,3-diones[37].

In order to further explore the potential of chiral 2,3-olefinic acetals in organic synthesis, we attempted our earlier procedure for converting the 2,3-olefinic acetals into 3-keto acetals via the reduction of epoxides with $LiAlH_4$ followed by chromium trioxide oxidations. However, reduction with $LiAlH_4$ (obtained from E. Merck) consistently gave 2-hydroxy acetal instead of 3-hydroxy acetal in the case of both chiral as well as achiral epoxides. This reversal in the regioselectivity was surprising. The only difference in the reaction conditions had been in using $LiAlH_4$ obtained from different sources. The $LiAlH_4$ obtained from either of the sources was used as solid and no attempts were made to use ethereal solution. However it was noted that with $LiAlH_4$[38] (ex: SRL), a large excess of it was required for complete disappearance of the starting epoxide.



SCHEME-16

It was therefore suspected that the impurities present in $LiAlH_4$ may have caused isomerisation of epoxides to 3-keto acetals, which upon reduction, gave the corresponding 3-hydroxy acetals (Figure 3).



M = Metal impurity

Fig. 3

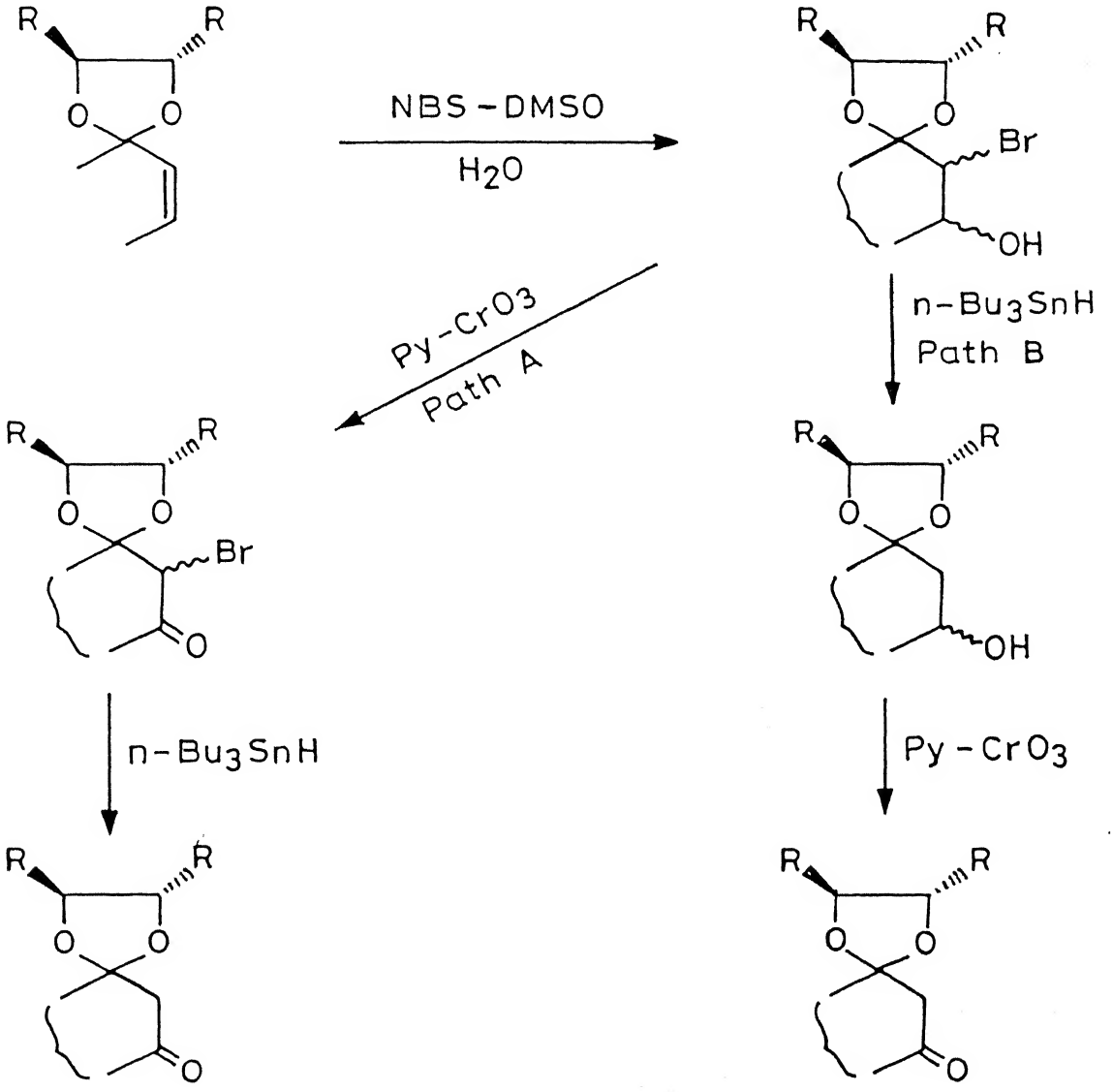
One of the crucial ways of judging if the compound is a 2-hydroxy or a 3-hydroxy acetal is to examine the ^1H NMR spectrum of the corresponding keto acetal. In the case of 3-keto acetals, the characteristic singlet for the methylene protons sandwiched between the acetal and the carbonyl group is observed at δ 2.65. This singlet, as expected, is absent in the case of 2-keto acetals.

It may be noted that chiral 2-keto acetals have already been found[39] to give very high degree of diastereoselectivity during Grignard additions, which result in the formation of chiral 2-alkyl, 2-hydroxy cycloalkanones. In view of this, the present route to 2-keto acetals is expected to be useful.

Further, in the synthesis of (+)-Pedamide, Matsumoto et al[23] have observed high degree of diastereoselectivity in $LiAlH_4$ reduction of chiral 3-keto acetals which constituted the key step in this synthesis. Thus, alternate routes to 2-keto as well as 3-keto acetals would be useful. In the present study, we have explored new approaches to these compounds.

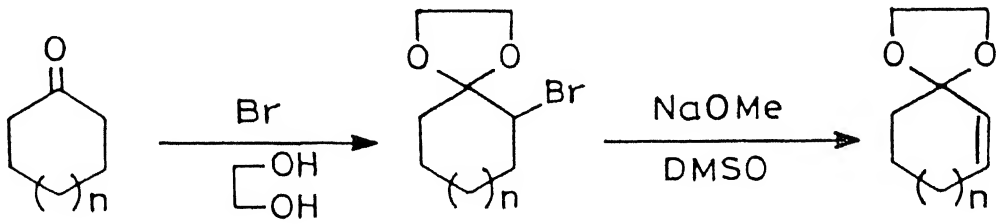
During our earlier studies[37] it was noted that while epoxidations of 2,3-olefinic acetals generally took place with m-CPBA, 2,3-cyclopentene acetals were unreactive towards it. However, we had synthesised these epoxides in two steps via their 'bromohydrins' (Scheme 17) followed by base treatment. The study of regiochemistry of bromohydrins was unimportant in view of the epoxide formation. In view of the problems associated with $LiAlH_4$ reduction and our interest in continuing studies with 3-keto acetals, we decided to study the regiochemistry of these bromohydrins and to find out if they could be converted into 3-keto acetals. For this purpose, we began our study with achiral 2,3-olefinic acetals first. Indeed, we have found that debromination with n-Bu_3SnH followed by Py-CrO_3 oxidation gave only 3-keto acetals (Path-B; Scheme 17). This indicated that bromohydrin formation had been highly regioselective reaction in the present study. Alternatively, oxidation of bromohydrins to

bromoketones (Path A; Scheme 17) followed by debromination with n-Bu_3SnH led to the formation of 3-keto acetals. These 3-keto acetals could be hydrolysed under standard conditions to yield 1,3-diones. Three different 1,3-diones (cf. entries 2, 3 and 4; Table 1) were synthesised in this manner.



SCHEME 17

All the achiral olefinic acetals, required for the above mentioned studies, were prepared according to a reported method[40] of bromoacetalisation followed by debromination with NaOMe in DMSO (Scheme 18) and were thoroughly characterised spectroscopically and analytically (cf. experimental section).

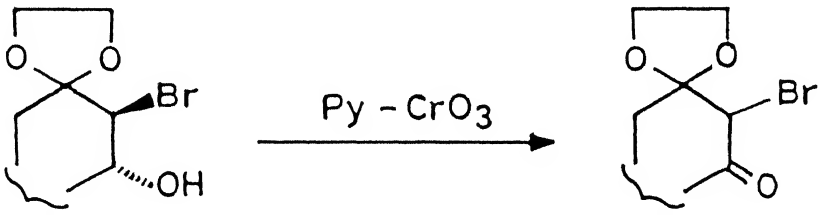


SCHEME - 18

Achiral 2,3-olefinic acetals were then subjected to bromohydrin formation with NBS/DMSO-H_2O reagent system to yield 2-bromo, 3-hydroxy alkanone acetals as the only regioisomer, in each case studied, in excellent yields. For example, 2,3-cyclohexenone ethylene acetal 75 (cf. Table 1) furnished 2-bromo, 3-hydroxy cyclohexanone ethylene acetal 80 in 89% yield. Its IR spectrum showed an absorption at 3460 cm^{-1} corresponding to -OH group and its ^1H NMR spectrum had peaks at δ 4.45-3.7 (6H, m, $-OCH_2CH_2O-$, $>CHBr$, $>CHOH$), 2.67 (1H, br s, -OH) and 2.37-1.27 (6H, m, 3X $-CH_2-$). Mass spectrum of this compound gave a molecular ion peak m/z at 236. Likewise, similar pattern was observed in the case of other cyclic acetals. 3-Pentenone ethylene acetal 78 gave 1-hydroxy, 2-bromo pentane-3-one acetal 83 as the only product. As expected, its IR spectrum showed an absorption at 3450 cm^{-1} and its ^1H NMR spectrum had signals at δ

4.27-3.67 (7H, m, $-OCH_2CH_2O-$, $-C\underline{H}_2OH$, $\rangle CHBr$), 2.9 (1H, s, -OH), 2.33-1.37 (2H, m, $-C\underline{H}_2CH_3$), 0.9 (3H, t, J = 7 Hz, $-CH_2C\underline{H}_3$). Other achiral 2,3-olefinic acetals viz. 74, 76, 77 gave the corresponding bromohydrins 79, 81, 82 respectively and their spectral data was in complete agreement with the structures assigned to them (cf. experimental section).

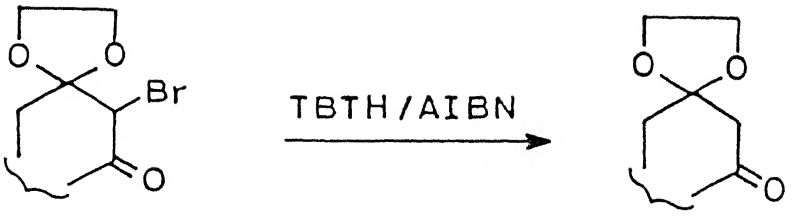
Oxidation of bromohydrins with CrO_3-Py reagent system furnished the corresponding bromoketones (Scheme 19) in moderate to good yields (cf. Table I). For example, 2-bromo, 3-hydroxy cyclohexanone ethylene acetal 80 upon oxidation furnished 2-bromo 3-oxo cyclohexanone ethylene acetal 84 in 65% yield. Its IR



SCHEME -19

spectrum showed absorption at 1720 cm^{-1} for $-\overset{O}{\overset{\|}{C}}-$ group and ^1H NMR spectrum had signals at δ 4.17-3.77 (5H, m, $\rangle CHBr$, $-OCH_2CH_2O-$), 3.33-1.4 (6H, m, methylenes). Similarly other bromohydrins 81 and 82 gave bromoketones 85 and 86 respectively.

These bromoketones viz. 84, 85 and 86 upon treatment with $n\text{-}Bu_3SnH$ in refluxing benzene in the presence of catalytic amount of AIBN have undergone reductions (Scheme 20) smoothly to furnish 3-keto acetals 91, 92 and 93 respectively in good yields (cf. Table 1).

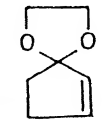
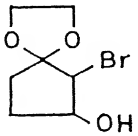
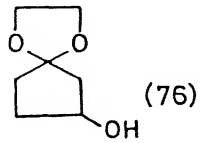
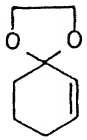
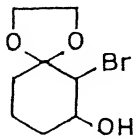
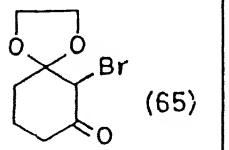
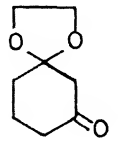
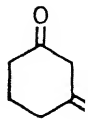
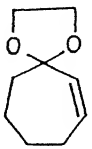
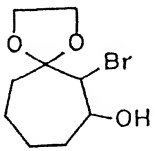
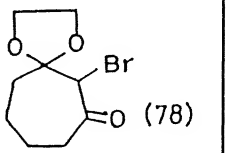
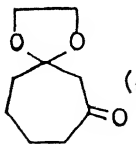
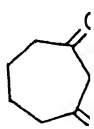
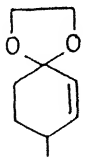
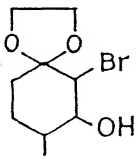
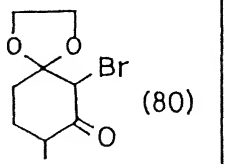
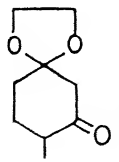
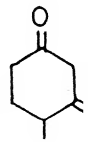
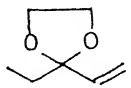
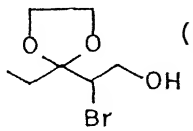
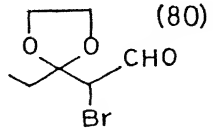
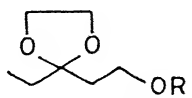
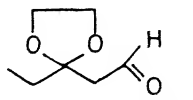


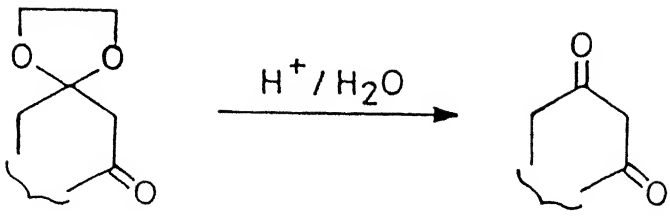
SCHEME-20

The characteristic singlet in their ^1H NMR spectra for the two methylene protons sandwiched between the carbonyl group and acetal group were present in all the cases. Thus, 3-oxo cyclohexanone ethylene acetal 91 had the following signals in its ^1H NMR spectrum : δ 3.83 (4H, s, $-OCH_2CH_2O-$), 2.37 (2H, s, $-\overset{O}{\overset{\|}{C}}-CH_2-$ with two $-O-$ groups), 2.3-1.93 (2H, m, $-\overset{O}{\overset{\|}{C}}-CH_2-CH_2-$), 1.93-1.6 (4H, m, 2X, $-CH_2-$). It showed absorption in its IR spectrum at 1720 cm^{-1} and its mass spectrum had molecular ion peak m/z at 156 corresponding to its molecular weight.

But unfortunately in the case of cyclopentanone, the corresponding bromo ketone as well as the 3-keto acetal could not be obtained in pure form and attempts to purify these compounds by column chromatography were unsuccessful. Likewise, although 83, obtained from 3-pentanone, could be oxidised to 87, its further reduction was not clean. So in this case, the bromohydrin 83 was first reduced to the corresponding 3-hydroxy compound, i.e., 89 which could be oxidised to 94 in good yield. The 3-keto acetals viz. 91-93 were then hydrolysed (Scheme 21) to obtain the corresponding 1, 3-diones in good yield (cf. Table 1). Hydrolysis of 94, however, was not clean. These diones were characterised rigorously and compared with the authentic samples.

Table 1

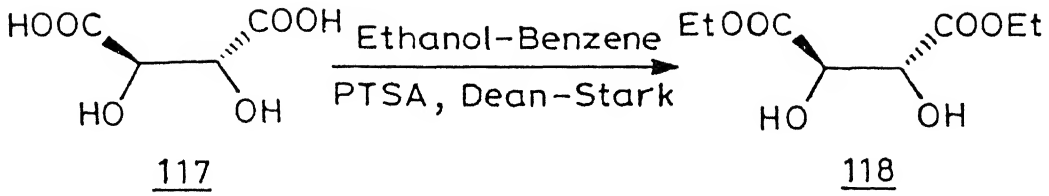
Entry	2,3-Olefinic acetal (% Yield)	Bromohydrin (% Yield)	Bromoketone (% Yield)	3-Hydroxy acetal (% Yield)	3-Keto acetal (% Yield)	1, 3-Dion (% Yield
1	 74 (56)	 79 (81)	—	 88 (76)	—	—
2	 75 (72)	 80 (89)	 84 (65)	—	 91 (81)	 95
3	 76 (87)	 81 (93)	 85 (78)	—	 92 (88)	 96
4	 77 (80)	 82 (87)	 86 (80)	—	 93 (85)	 97
5	 78 (79)	 83 (83)	 87 (80)	 89 R = H (89) 90 R = OH (77)	 94 (83)	—



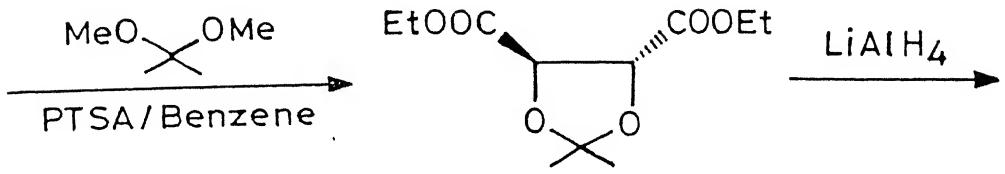
SCHEME-21

For the synthesis of chiral 2,3-olefinic acetals, chiral 1,2-diol used was compound 121, which was prepared from 2R, 3R(+)-tartaric acid 117 (Scheme 22). Bromo dimethyl acetals 122 and 123 of cyclopentanone and cyclohexanone were exchanged with the diol 121 to obtain the corresponding chiral 2-bromo acetals 124 and 125 respectively. Elimination of HBr from these compounds with NaOMe in DMSO resulted in the formation of 2,3-olefinic acetals 98 and 99 (Scheme 22). The spectral data obtained for these compounds was in complete agreement with the structures assigned to them (cf. experimental section). These chiral 2,3-olefinic acetals 98 and 99 also gave only one regioisomer, but as a diastereomeric mixture, on treatment with NBS/DMSO-H_2O. The two chiral bromohydrins 100 and 101 were converted into epoxides by treatment with NaH in THF.

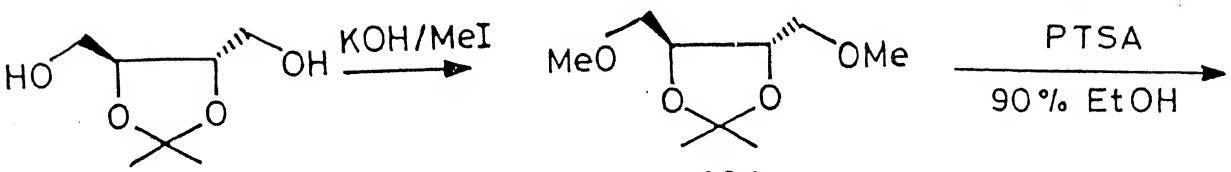
The two diastereomers A and B (Scheme 23) of the epoxides 102 and 103 were inseparable on thin layer chromatography. A combination of different solvent systems and slow purification by column chromatography also did not result in the separation of these diastereomers. Hence, the epoxide obtained was used as such. The ^1H NMR spectral analysis of 102 showed signals at δ 4.15-3.85 (2H, m, methines) 3.7-3.27 (11H, m, 2X $-CH_2OCH_3$ and C_3-H), 3.17, 3.07 (1H, two d, J = 3 Hz) and 2.1-1.4 (4H, m, 2X



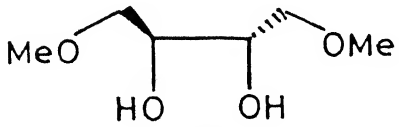
117 118



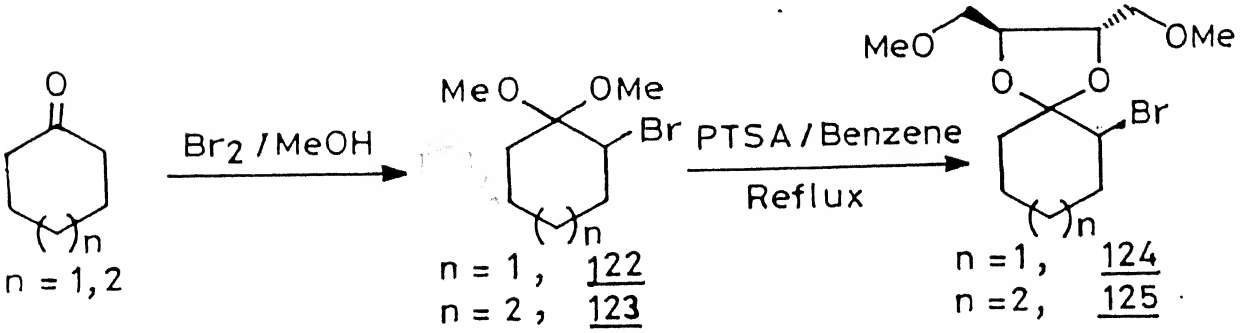
119

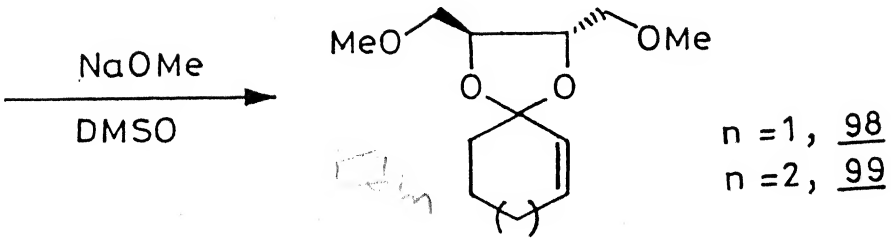


120 120A



121

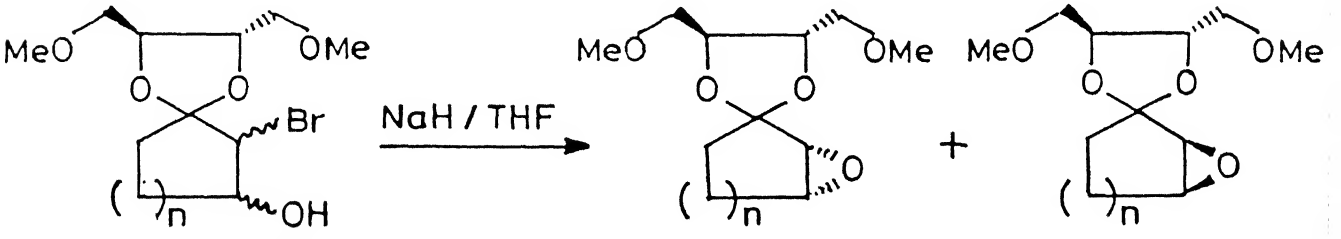




SCHEME-22

$-CH_2-$). The presence of two doublets at δ 3.17 and 3.07 in the ^1H NMR spectrum of this epoxide accounting for one proton was expected due to the presence of two diastereomers. From the integration values of these two peaks it appeared that the two diastereomers were present in almost equal amounts.

Similarly, 2,3-epoxy cyclohexene-1-one chiral acetal 103 obtained by base treatment of the corresponding bromohydrin or with m-CPBA in refluxing CH_2Cl_2 showed ^1H NMR signals at δ 4.18-3.93 (2H, m, methines), 3.7-3.2 (11H, m, containing a singlet at δ 3.4, 2X $-CH_2OMe$ and C_3-H), 3.12, 3.02 (1H, two d, J = 3 Hz) and 2.0-1.37 (6H, m, 3X $-CH_2-$). The appearance of two doublets at δ 3.12 and 3.02 in the ^1H NMR spectrum of this epoxide accounting for one proton was again indicative of the presence of two diastereomers.

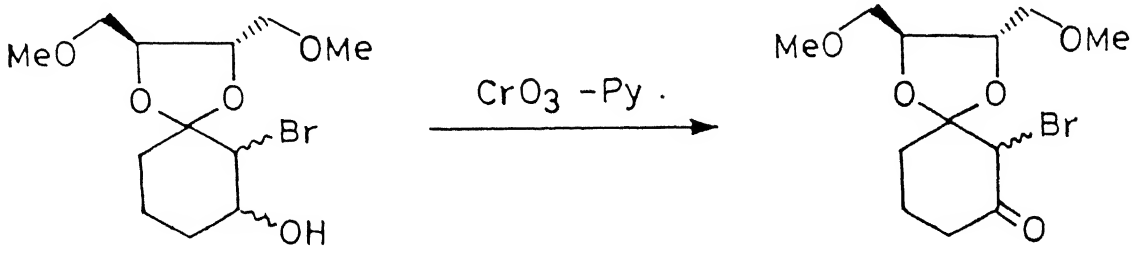


n = 1 100
n = 2 101

n = 1 102
n = 2 103

SCHEME-23

Oxidation of these chiral bromohydrins 100 and 101 was attempted. Although 101 could be converted into 104 in 71% yield, the corresponding cyclopentanone compound 100 could not be oxidised cleanly (Scheme 24). On the other hand, reduction of the

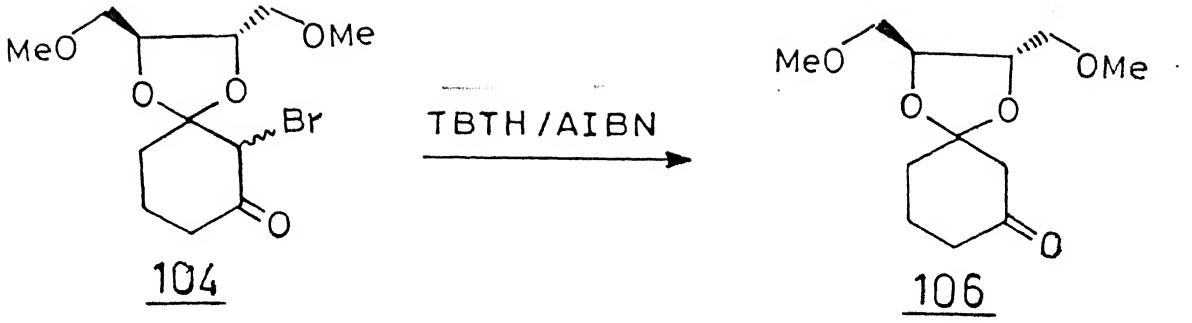


101 104

SCHEME-24

bromohydrin 101 with n-Bu_3SnH, followed by oxidation with Py-CrO_3 was clean and the corresponding 3-keto acetal 106 could be obtained in good yield. Reduction of the bromo ketone 104 was possible and the 3-keto acetal 106 could also be obtained via this route (Scheme 25). The above study has therefore led to the formation of 3-keto acetals in a regioselective manner. The chiral bromo ketone 104 gave 3-keto acetal 106 in 78% yield. In the IR spectrum, the compound 106 showed absorption at 1720 cm^{-1} for $-\overset{O}{\overset{\|}{C}}-$ group and its ^1H NMR spectrum showed peaks at δ 4.16-3.97 (2H, m, 2 methines), 3.5 (4H, d, J = 3.75 Hz, 2X $-CH_2OCH_3$), 3.44 (6H, s, 2X $-OCH_3$), 2.65 $\left(2H, s, -\overset{O}{\overset{\|}{C}}-CH_2-C\begin{matrix}O-\\O-\end{matrix}\right)$, 2.43-1.63 (6H, m, 3X $-CH_2-$). Mass spectrum reveals molecular ion peak m/z at 244 corresponding to its molecular weight.

After obtaining 3-keto acetals, we diverted our attention to obtain chiral 2-keto acetals. For this purpose, $LiAlH_4$ reduction



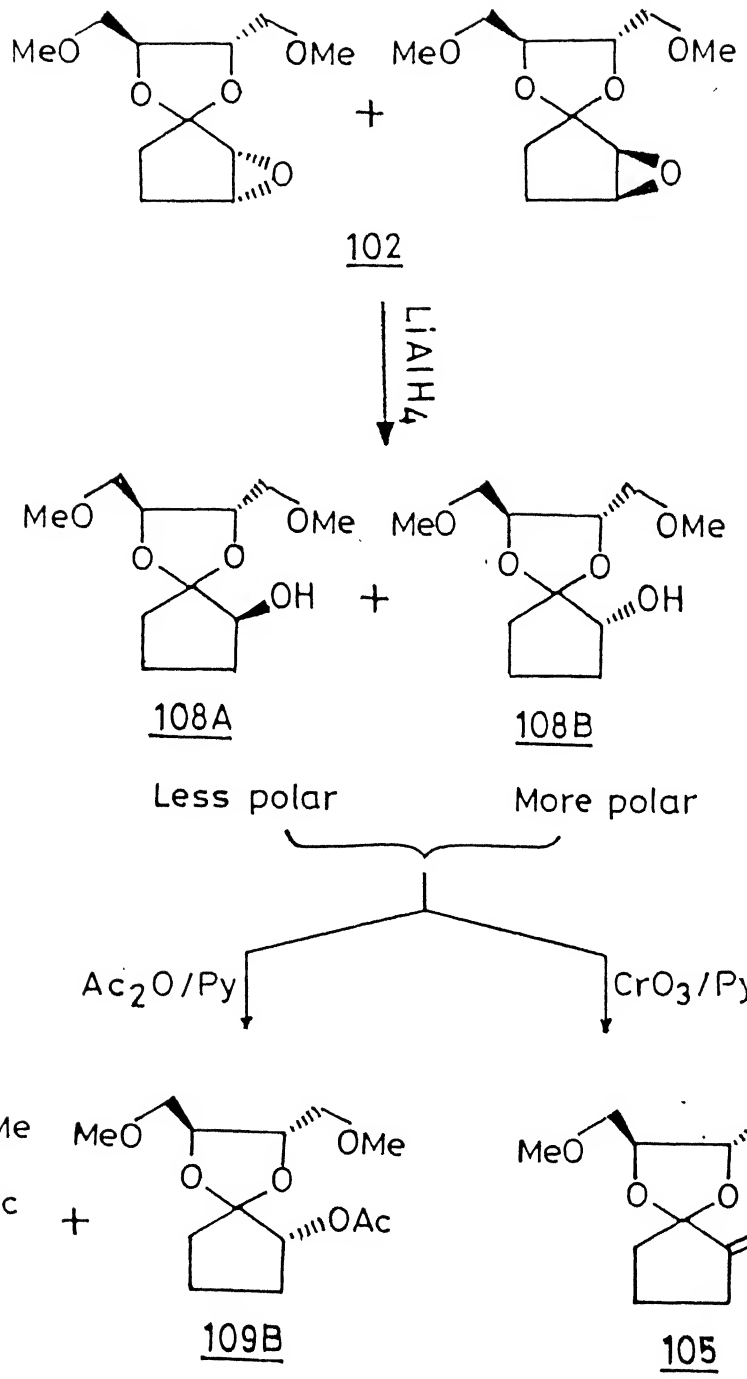
104 106

SCHEME - 25

was employed based on our new observation. Thus, epoxide 102 upon reduction with $LiAlH_4$ gave two alcohols 108A and 108B which were easily separated by column chromatography. Separate oxidation of these alcohols resulted in the formation of the ketone 105 (Scheme 26).

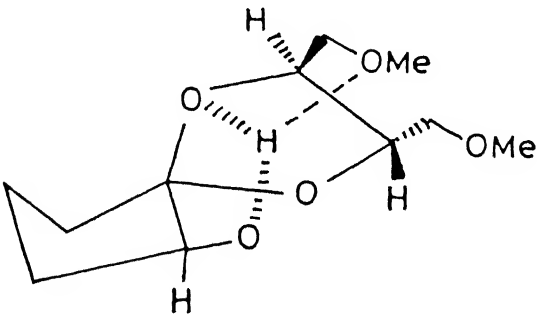
On the other hand, their acetylation products viz. 109A and 109B were inseparable on thin layer chromatography in different solvent systems. In the ^1H NMR spectrum, the higher R_f alcohol 108A showed signals at δ 4.3-3.73 (3H, m, methines), 3.7-3.2 (10H, m, with splitting of the $-OCH_3$ signal, 2X $-CH_2OCH_3$), 2.5 (1H, br s, -OH) and 2.03-1.37 (6H, m, 3X $-CH_2-$). The compound with lower R_f value 108B also exhibited almost similar spectral characteristics. The only observable difference in the ^1H NMR spectra of 108A and 108B was a slight variation in the splitting pattern of the signals, with a singlet at δ 3.4 for $-OCH_3$ protons in the case of 108B whereas two $-OCH_3$ signals in the case of 108A.

As mentioned above, the oxidised compounds obtained from both the alcohols were the same, i.e., compound 105. Its ^1H NMR spectrum showed signals at δ 4.05-3.8 (2H, m, methines), 3.67-3.3 (10H, m, containing a singlet at δ 3.5, 2X $-CH_2OCH_3$) and 2.4-1.6

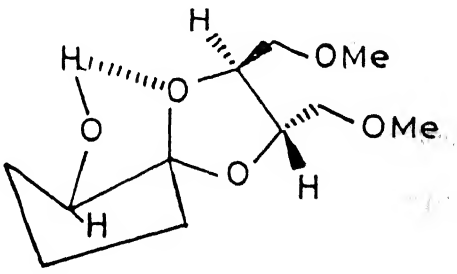

MeO
OMe
O
O
O
+
MeO
OMe
O
O
O
102
LiAlH4
MeO
OMe
O
O
OH
+
MeO
OMe
O
O
OH
108A
108B
Less polar
More polar
Ac2O/Py
CrO3/Py
MeO
OMe
O
O
OAc
+
MeO
OMe
O
O
OAc
MeO
OMe
O
O
O
109A
109B
105

SCHEME-26

(6H, m, 3X -CH_2-). The fact that the spectral data obtained fo the oxidised products of the two alcohols 108A and 108B i superimposable confirmed that the two alcohols were diastereomers The inseparability of the two acetates 109A and 109B on thin laye: chromatography and column chromatography was not surprising. Thi: was because recently Mash and Hemperly[41] have found simila: polarity differences between these two diastereomers prepared fro: α-hydroxy cyclopentanone 1,4-di-O-benzyl-L-threitol acetals but the corresponding methyl ethers were found to be chromatographically inseparable. They rationalised their observation by invoking intramolecular hydrogen bonding arrays between the proximal dioxolane and appendage oxygen atoms with the α-hydroxyl group. In one of the diastereomers, such a hydrogen bonding is possible (cf. 108A) which renders it to be less polar than the other isomer in which hydrogen bonding is only possible with one of the acetal oxygens.



108 A



108 B

FIGURE 4

Similar rationalisation is evidently applicable in the present study also for 108A and 108B (Figure 4) and to account for the chromatographic inseparability of the corresponding acetates. Due to these differences in the extent of hydrogen bonding, the

$-OCH_3$ protons in 108A are found as two separate singlets, whereas in 108B they appear as a single peak.

Reduction of the keto acetal 105 with $LiAlH_4$ at $-78^{\circ}C$ gave only one compound 108C and the ^1H NMR spectrum of this compound was exactly identical with that of one of the diastereomeric alcohols i.e. the less polar one obtained from epoxide reduction. It is possible to explain the preferential formation of 108C through the transition state as shown in Figure 5.

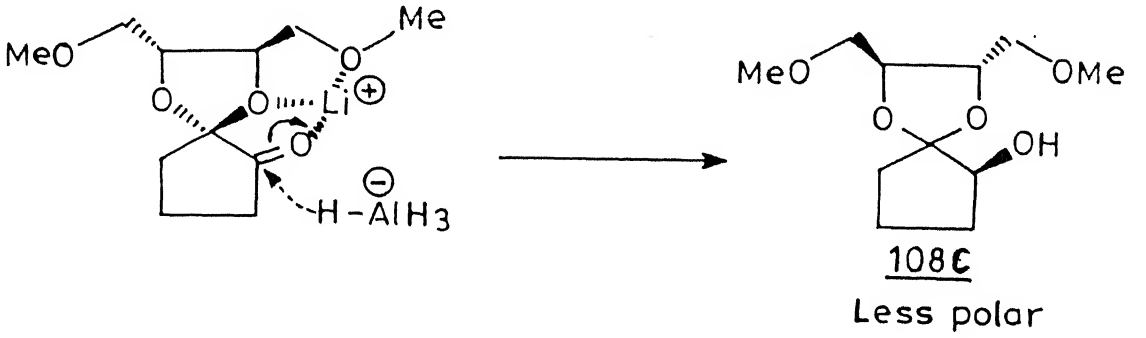
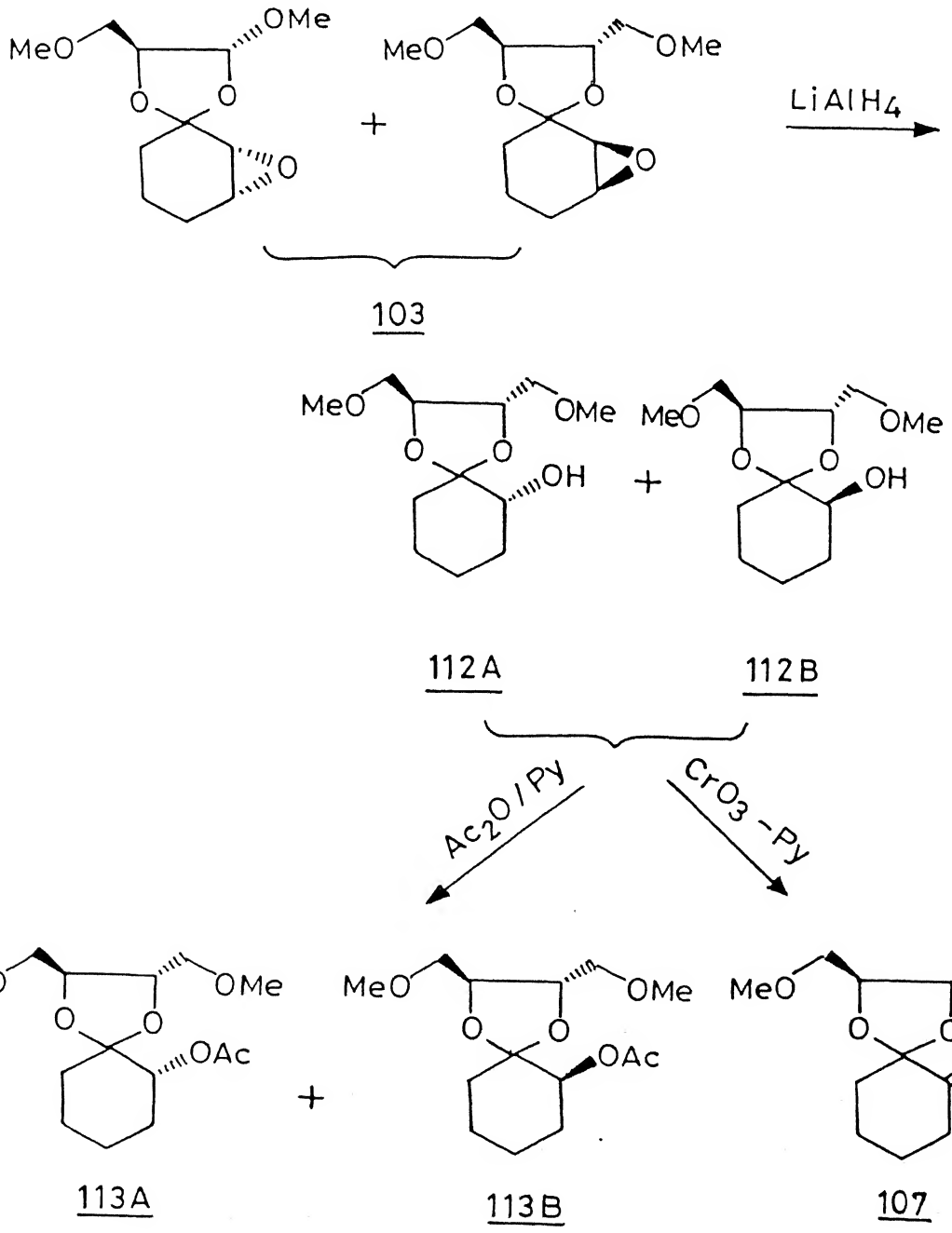


FIGURE 5

The presence of only one diastereomer was further confirmed on the basis of 400 MHz ^1H NMR spectral analysis of the corresponding acetate 109 in the presence of $Eu(hfc)_3$.

On the other hand, when the diastereomeric mixture of the epoxide 103 (derived from cyclohexanone system) was reduced with $LiAlH_4$, chromatographically inseparable mixture of the two diastereomers 112A and 112B was obtained. This was evident from the analysis of the ^1H NMR spectrum of the product. Thus, the multiplet at δ 3.67-3.3, corresponding to ten protons, was found to contain two singlets at δ 3.4 and 3.37 of equal intensities.

Mash and Hemperly[41] have also observed a somewhat similar behaviour of diastereomeric α-hydroxy cyclohexanone 1,4-di-O-benzyl-L-threitol acetals. The inseparability of the diastereomers has been attributed to the averaging of the various possible hydrogen bonded forms due to cyclohexane ring inversion. This results in an extremely small difference in polarity to be of any significance for chromatographic separation. Thus, our results confirm the observations of Mash and Hemperly.



SCHEME-27

Acetylation of alcohol (i.e., diastereomeric mixture of 112A and 112B) gave a diastereomeric mixture of 113A and 113B (Scheme 27). The $-OCH_3$ signal in the ^1H NMR spectrum displayed a single peak for the $-OCH_3$ groups.

Oxidation of the mixture of 112A and 112B with CrO_3-Py reagent system gave the ketone 107 in 78% yield. The ^1H NMR spectrum of 107 showed signals at δ 4.1-3.83 (2H, m, methines), 3.65-3.3 (10H, m, 2X $-CH_2OCH_3$), 2.63-1.5 (8H, m, 4X $-CH_2-$). The IR spectrum showed absorption at 1710 cm^{-1} for $-\overset{O}{\overset{\|}{C}}-$ streching and in the mass spectrum a peak was observed at m/z 244 for the molecular ion (M^+).

Reduction of the ketone 107 with $LiAlH_4$ at 0^oC followed by acetylation gave the acetate 113C (Figure 6) as a mixture of two diastereomers in the ratio 75:25 as revealed by its ^1H NMR spectrum in the presence of $Eu(hfc)_3$. On the basis of observations made in the cyclopentane series, it is possible to extrapolate here that the major diastereomer is 112B (analogous to 108C) and the minor one is 112A.

The 2-keto acetal 105 obtained by the oxidation of either of the alcohols 108A or 108B gave a single compound 114 upon treatment with MeMgI, homogeneous on thin layer chromatography. Its ^1H NMR spectrum showed signals at δ 4.0-3.8 (2H, m, methines), 3.7-3.1 (10H, m, contains a singlet at δ 3.27, 2X $-CH_2OCH_3$), 1.97 (1H, br s, -OH), 1.83-1.4 (6H, m, methylenes). IR spectrum showed absorption at 3450 cm^{-1} and mass spectrum contained molecular ion peak at m/z 246. Formation of a single product 114 chromatographically, coupled with the fact that its ^1H NMR

spectrum shows a singlet for the two $-OCH_3$ groups, are important points to be considered. Our earlier observation that the two diastereomeric alcohols 108A and 108B were chromatographically separable and the alcohol 108B (the more polar of the two involving no intramolecular hydrogen bonding) showed a single peak for the two $-OCH_3$ groups, whereas 108A with its hydrogen bonding, showed two separate signals for the two $-OCH_3$ groups, is an aspect worth comparison with the spectral data obtained for the alcohol 114. If 114 was a mixture of diastereomers, $-OCH_3$ signals would not have appeared together. Further, the two diastereomers in this case would have been chromatographically separable. These observations indicate that the compound 114 is predominantly a single diastereomer involving no hydrogen bonding. High resolution 400 MHz ^1H NMR study using shift reagent $Eu(hfc)_3$ also indicated this prediction of high diastereoselectivity (95:5). Based on above observations, the configuration of the major diastereomer could be written as shown in Figure 6.

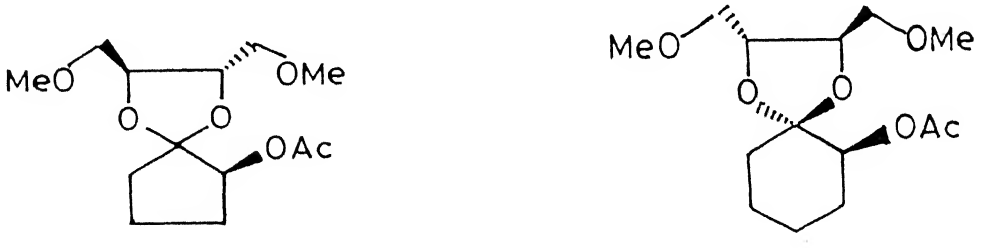
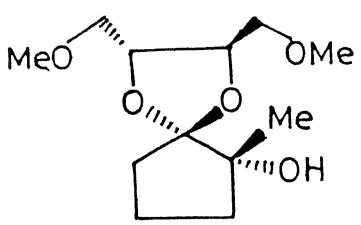


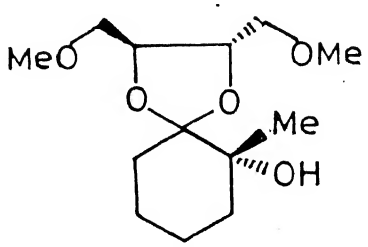
FIGURE 6

In the cyclohexane system, the reaction of the ketone 107 with MeMgI gave 2-hydroxy, 2-methyl cyclohexanone acetal 116 in 80% yield. The ^1H NMR spectrum of this tertiary alcohol showed

signals at δ 4.13-3.9 (2H, m, methines), 3.6-3.27 (10H, m, containing a singlet at δ 3.4, 2X $-CH_2OCH_3$), 2.3 (1H, br s, -OH), 2.07-1.6 (8H, m, methylenes), 1.27 and 1.13 (3H, 2s, $-\overset{|}{\underset{|}{C}}-CH_3$). It is evident from ^1H NMR spectral data that the methoxy protons appeared as a sharp singlet at δ 3.4 thereby indicating that it is only a single diastereomer, and not a mixture of two diastereomers. By extending the same analogy as that for the formation of 2-hydroxy, 2-methyl cyclopentanone acetal 114 from the ketone 105, we could justify the formation of a single diastereomer 116 in this case also. It is likely that MeMgI attacks the carbonyl group from only one face resulting in the formation of an alcohol which involves no intramolecular hydrogen bonding with the methoxy oxygens of the appendage in the dioxolane ring. This would, therefore, not result in the magnetic non-equivalence of the protons of the two $-OCH_3$ groups. This is the reason for the observation of a single peak for the $-OCH_3$ protons. On the other hand, in the 400 MHz ^1H NMR spectrum in the presence of $Eu(hfc)_3$, the protons of the two $-OCH_3$ groups showed some separation accounting for 96:4 ratio of the two diastereomers. Thus on the basis of earlier arguments, the major diastereomer could be assigned the configuration as given in Figure 7.



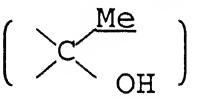
114

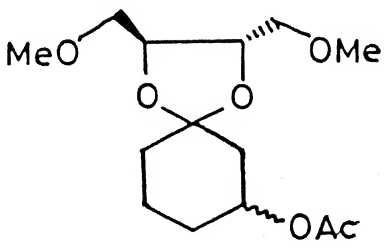


116

FIGURE 7

In case of reactions of 3-keto systems, the diastereoselectivity was low. $LiAlH_4$ reduction of 106 yielded 3-hydroxy cyclohexanone acetal 110 in 82% yield. In the ^1H NMR spectrum, 110 showed signals at δ 3.93-3.53 (3H, m, methines), 3.4 (4H, d, J = 3 Hz, 2X-$C\underline{H}_2OCH_3$), 3.27 (6H, s, 2X-OCH_3), 2.93 (1H, br s, -OH), 1.94-1.1 (8H, m, methylenes). Upon acetylation with Py-Ac_2O, the corresponding acetate 111 was obtained in 82% yield whose ^1H NMR spectrum showed signals at δ 4.67 (1H, m, -CHOAc), 3.83 (2H, m, methines), 3.4 (10H, br s, 2X-CH_2OCH_3), 1.93 (3H, s, -$OCOCH_3$), 2.06-1.26 (8H, m, methylenes). Its 400 MHz ^1H NMR spectrum in the presence of $Eu(hfc)_3$ showed two peaks corresponding to acetate in the ratio of 67:33.

Similarly, addition of MeMgI to 106 yielded the tertiary alcohol 115 whose ^1H NMR analysis showed signals at δ 3.93 (2H, m, methines), 3.6-3.27 (10H, m, containing a singlet at δ 3.4, 2X-CH_2OCH_3), 2.3 (1H, br s, -OH), 2.7-1.6 (8H, m, methylenes), 1.27 and 1.33 (3H, 2s, -C(CH$_3$)-). 400 MHz ^1H NMR spectrum in the presence of $Eu(hfc)_3$ showed it to be a mixture of two diastereomers in the ratio of 65:35. The methyl group  appeared as two singlets corresponding to the two diastereomers (Figure 8).



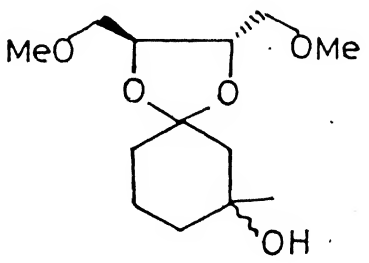
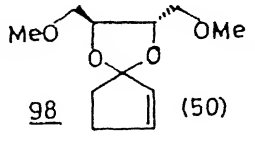
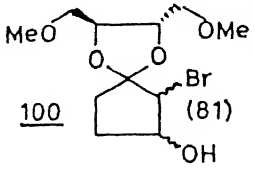
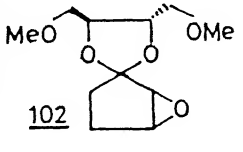
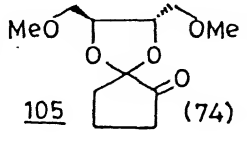
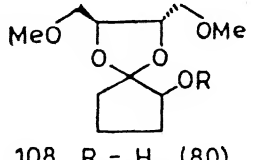
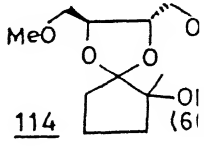
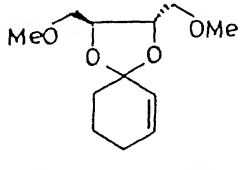
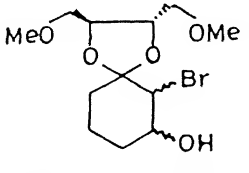
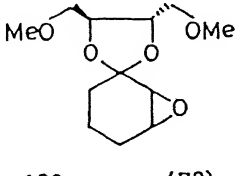
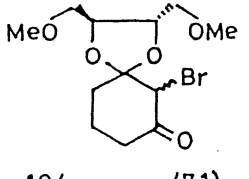
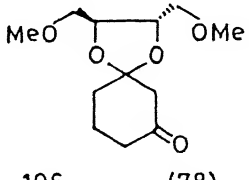
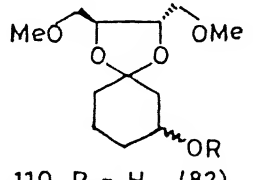
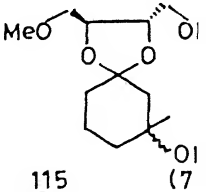
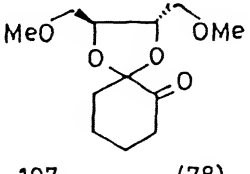
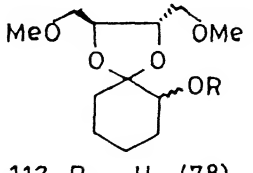
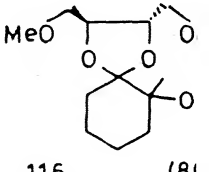


FIGURE 8

Clearly, the $LiAlH_4$ reduction as well as the Grignard reaction is not highly diastereoselective with 3-keto acetal 106. It is likely that the carbonyl group in 3-keto acetal system being one more carbon away from the acetal moiety compared to 2-keto acetal system, offers much less coordination of the metal simultaneously with it as well as with the acetal oxygens. This appears to be particularly the case with cyclic systems where conformational rigidity prevents such proximity. In acyclic systems such as those studied by Matsumoto et al[23], high diastereoselectivity is possible as a result of simultaneous metal ion coordination.

TABLE 2

Entry	2,3-Olefinicacetal (% Yield)	Bromohydrin (% Yield)	Epoxide (% Yield)	Bromoketone (% Yield)	Ketoacetal (% Yield)	Hydroxyacetal (% Yield)
1	 98 (50)	 100 (81)	 102	—	 105 (74)	 108 R = H (80) 109 R = OAc (79)  114 (6
2	 99 (66)	 101 (81)	 103 (78)	 104 (71)	 106 (78)	 110 R = H (82) 111 R = OAc (82)  115 (7
					 107 (78)	 112 R = H (78) 113 R = OAc (82)  116 (8

I.A.3 EXPERIMENTAL

All the reactions were performed in oven dry glass apparatus. Reaction mixtures were stirred magnetically, unless otherwise specified.

Commercial grade solvents were distilled before use. Petroleum ether used was the fraction 60-80^{o}C. Ethylene glycol was dried by storing over anhydrous potassium carbonate and distilling under vacuum. Dichloromethane used for the reactions was distilled over phosphorous pentoxide (P_2O_5). Dimethyl sulfoxide was dried by freezing it at 5^{o}C, removing the unfrozen liquid, distilling from calcium hydride (CaH_2) under vacuum and finally storing over Type 4A^{o} molecular sieves. Sodium dry diethyl ether and tetrahydrofuran were distilled over lithium aluminium hydride before use in reactions. Acetic anhydride was distilled over P_2O_5. Pyridine was dried by refluxing over potassium hydroxide pellets for 2h and distilling therefrom. Benzene was dried by first shaking with fused calcium chloride ($CaCl_2$), distilling and finally storing over sodium wires. N-Bromosuccinimide was recrystallized from water and dried in a dessicator over fused $CaCl_2$. Magnesium turnings were activated prior to use. Chromium trioxide was dried over P_2O_5 in a vacuum dessicator.

Thin layer chromatography (TLC) was performed on prepared thin layers of E. Merck Silica gel-G on microscope slides. Visualization of the spots was effected by ultraviolet illumination or expsoure to iodine vapour. Preparative TLC plates were prepared from a slurry of 20g of E. Merck Silica get-G in 45

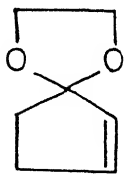
General Procedure for the Preparation of Achiral Olefinic Acetals

To a stirred solution of 40 mmol of a cycloalkanone in 50 ml of anhydrous ethylene glycol at room temperature was added a small portion of bromine. The solution was warmed slightly so that the uptake of bromine was complete. The remaining 6.4 gm (40 mmol) of bromine was then added at 15-20^{o}C in the case of cyclopentanone (and at 35-40^{o}C in other cases) at such a rate that a faint colouration of bromine was maintained at all the time. After stirring for additional 10 minutes, the reaction mixture was poured into a stirred suspension of 10 gms of anhydrous sodium carbonate in 40 ml of petroleum ether (60-80^{o}C) cooled in an ice-water bath. After continuing the stirring for 5 minutes, 50 ml of water was added to it. The organic layer was separated and the aqueous layer was extracted with petroleum ether (3x30 ml). The combined organic layer was washed with water (2x15 ml), brine (15 ml) and dried over anhydrous sodium sulphate. The solvent was evaporated under reduced pressure to obtain the 2-bromoacetals which were directly used for dehydrobromination as described below.

Sodium methoxide (2.6 gm, 48 mmol) was stirred in dry DMSO (25 ml) at 40^{o}C until a homogeneous mixture was obtained. A bromoacetal (40 mmol) was then added dropwise to it at ca 20^{o}C over a period of 30 minutes and the stirring was continued at room temperature for additional 8 hours. The reaction mixture was then slowly poured into 100 ml of ice-cold water with stirring and extracted with diethylether (4x50 ml). The combined ether extract was washed with water (2x50 ml), brine (50 ml) and dried over

anhydrous sodium sulphate. Ether was removed at the rotary evaporator and the crude 2,3-olefinic acetal was purified by Kugelrohr distillation.

2-Cyclopentenone ethylene acetal 74



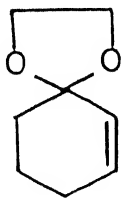
Overall yield : 56 %

b.p. : 115°C/30 mm (Lit.[41] b.p. : 64-65°C/22 mm)

IR spectrum (neat) ν_{max} : 1620 (C=C), 1170, 1140, 1060 cm^{-1}

^1H NMR spectrum (CCl_4) : δ 1.8-2.1 (2H, m, $-CH_2-$), 2.2-2.53 (2H, m, allylic), 3.83 (4H, s, $-O-CH_2-CH_2-O-$), 5.47-5.7 (1H, m, olefinic C_2-H), 5.87-6.07 (1H, m, olefinic C_3-H).

2-Cyclohexenone ethylene acetal 75



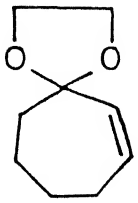
Overall yield : 72%

b.p. : 100°C/25 mm (Lit.[41] b.p. : 86.5-88.5°C/23 mm)

IR spectrum (neat) ν_{max} : 1650 (C=C), 1170, 1110, 1060, 1030 cm^{-1}

^1H NMR spectrum (CCl_4) : δ 1.03-2.4 (6H, m, $3X-CH_2-$), 3.83 (4H, s, $-O-CH_2-CH_2-O-$), 5.27-5.5 (1H, m, olefinic C_2-H), 5.6-5.97 (1H, m, olefinic C_3-H).

2-Cycloheptenone ethylene acetal 76



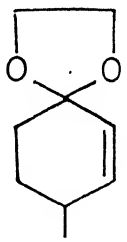
Overall yield : 87%

b.p. : 100-105°C/10 mm (Lit.[41] b.p. : 67°C/2.4 mm)

IR spectrum (neat) ν_{max} : 1650 (C=C), 1170, 1110, 1060, 1040 cm^{-1}

^1H NMR spectrum (CCl_4) : δ 1.4-2.5 (8H, m, 4X-CH_2-), 3.7-4.0 (4H, m, -O-CH_2-CH_2-O-), 5.4-6.0 (2H, m, olefinic).

4-Methyl-2-cyclohexenone ethylene acetal 77



Overall yield : 80%

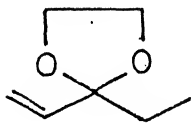
b.p. : 90°C/10 mm

IR spectrum (neat) ν_{max} : 1650 (C=C), 1180, 1120, 1060, 1040 cm^{-1}

^1H NMR spectrum (CCl_4) : δ 1.0 (3H, d, >CH-C<u>H</u>$_3$, J = 7 Hz), 1.42-2.32 (5H, m, >C<u>H</u> and 2X-CH_2-), 3.83 (4H, s, -O-CH_2-CH_2-O-), 5.37-5.9 (2H, m, olefinic).

Mass spectrum m/z : 154 (M^+)

1-Pentene-3-one ethylene acetal 78



Yield : 79%

b.p. : 100°C/30 mm

IR spectrum (neat) ν_{max} : 1630 (C=C) cm^{-1}

^1H NMR spectrum (CCl_4) : δ 0.83 (3H, t, $-CH_2-CH_3$, J = 7 Hz), 1.63 (4H, q, $-CH_2-CH_3$, J = 7 Hz), 3.77 (4H, s, $-O-CH_2-CH_2-O-$), 4.8-5.83 (3H, m, olefinic).

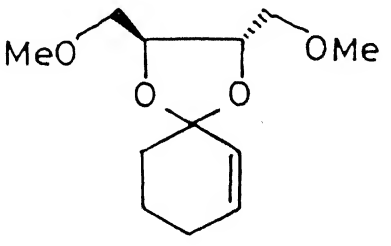
Mass spectrum m/z : 128 (M^+)

General Method for the Preparation of Chiral 2,3-Olefinic Acetals

To a solution of 20 mmol of cycloalkanone in 25 ml of dry methanol was added a small portion of bromine at room temperature. The solution was warmed slightly so that the uptake of bromine was complete. The remaining 3.2 gms (20 mmol) of bromine was then added at 35-40°C at such a rate that a faint colouration of bromine was maintained at all times. After additional 10 minutes of stirring, the reaction mixture was poured into a stirred suspension of 2 gms of sodium methoxide in 20 ml of petroleum ether (40-60°C) cooled in an ice-water bath. After stirring for 5 minutes, 25 ml of cold water was added. Separation of the organic layer followed by extraction of the aqueous layer with petroleum ether (3x15 ml), drying of organic layer over anhydrous sodium sulphate and evaporation of the solvent under reduced pressure

gave the unstable 2-bromocycloalkanone dimethyl acetal. To this compound was added 3.2 gms (21.4 mmol) of the chiral diol 118 (cf. Experimental section for the preparation of chiral diol 118) and anhydrous PTSA (52 mg) in dry benzene (20 ml) and the mixture was refluxed for 2.5 hours. Neutralization of the reaction mixture with saturated sodium bicarbonate solution (10 ml), extraction with ether (3x30 ml) followed by usual workup gave the corresponding crude 2-bromoacetal. Sodium methoxide (650 mg, 12 mmol), was taken in dry DMSO (10 ml) and stirred at 40°c until a homogeneous mixture was obtained. The crude bromoacetal (5 mmol) obtained above was then added slowly to it at 20°C and then the whole mixture was stirred at 50°C for 10 hours. Usual workup, i.e., washing with ice-cold water, extraction with ether and evaporation of the organic layer gave the crude product which was purified by column chromatography [eluent : petroleum ether-ethyl acetate].

2-Cyclohexene-1-one cyclic (1S, 2S)-1,2-Bis(methoxymethyl) ethylene acetal 99



Yield : 66% (based on 2-bromocyclohexanone dimethyl acetal)

b.p. : 100-105°C/0.1 mm

IR spectrum (neat) ν_{max} : 3030, 1640 (C=C) cm^{-1}

^1H NMR spectrum (CCl_4) : δ 1.45-1.87 (4H, m, 2X-CH_2-), 1.87-2.15 (2H, m, allylic), 3.25-3.6 (10H, m, 2X-CH_2OCH_3), 3.77-4.03 (2H, m,

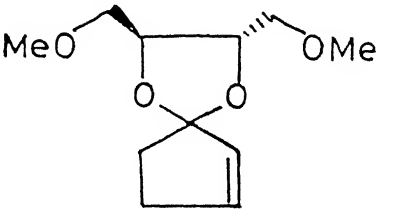
methines), 5.4-5.55 (1H, m, olefinic), 5.67-5.93 (1H, m, olefinic)

Mass spectrum m/z : 228 (M^+)

Anal. Calcd. for $C_{12}H_{20}O_4$: C, 63.13; H, 8.88

Found : C, 63.0; H, 8.68%

2-Cyclopentene-1-one cyclic (1S, 2S)-1,2-Bis (methoxymethyl) ethylene acetal 98



Yield : 50%

b.p. : 95-100°C/0.6 ml

IR spectrum (neat) ν_{max} : 3040 (C-H, vinylic), 1612 (C=C) cm^{-1}

^1H NMR spectrum (CCl_4) : δ 1.87-2.17 (2H, m, $-CH_2-$), 2.23-2.53 (2H, m, allylic), 3.3-3.7 (10H, m, containing a 6H singlet at δ 3.37, $2X-CH_2OCH_3$), 3.8-4.0 (2H, m, methines), 5.57-5.77 (1H, m, $C_2\underline{H}$), 5.85-6.1 (1H, m, $C_3\underline{H}$).

Mass spectrum m/z : 214 (M^+)

Anal. Calcd. for $C_{11}H_{18}O_4$: C, 61.66; H, 8.47

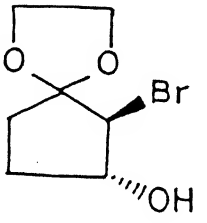
Found : C, 61.8; H, 8.5%

General Method for the Preparation of Bromohydrins from 2,3-Olefinic Acetals

An olefinic acetal (4 mmol) was treated with water (0.30 ml, 16 mmol) in DMSO (4 ml) and cooled to about 10°C. N-bromo-succinimide (890 mg, 5 mmol) was added to it in portions while

stirring. Stirring was continued for further 30 minutes at 10°C. A yellow coloured developed which deepened as the reaction progressed. The reaction mixture was then quenched with dil. aq. sodium bicarbonate (10 ml), with concomitant discharge of the yellow colour, followed by the extraction of the product into ether (4x20 ml). The combined ethereal layer was washed with cold water (10 ml), brine (10 ml) and dried over anhydrous sodium sulphate. Removal of the solvent gave a crude product which was purified by flash column chromatography [eluent : petroleum ether-ethyl acetate] to afford the pure bromohydrin.

Cyclopentenone ethylene acetal bromohydrin 79

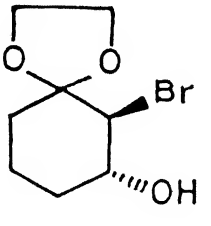


Yield : 81%

IR spectrum (neat) ν_{max} : 3460 (-OH) cm^{-1}

^1H NMR spectrum (CCl_4) : δ 1.33-2.47 (4H, m, 2X-CH_2-), 3.0 (1H, br s, -OH), 3.67-4.5 (6H, m, -O-CH_2-CH_2-O), >CHBr, >CHOH)

Cyclohexenone ethylene acetal bromohydrin 80



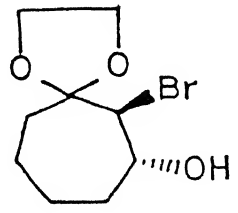
Yield : 89%

m.p. : 95^{0}C

IR spectrum (KBr) ν_{max} : 3460 (-OH) cm^{-1}

^{1}H NMR spectrum ($CDCl_3$) : δ 1.27-2.37 (6H, m, 3X-CH_2-), 2.67 (1H, br s, -OH), 3.7-4.45 (6H, m, -O-CH_2-CH_2-O-, >CHBr, >CHOH)

Cycloheptenone ethylene acetal bromohydrin 81

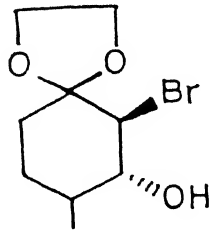


Yield : 93%

IR spectrum (neat) ν_{max} : 3460 (-OH) cm^{-1}

^{1}H NMR spectrum (CCl_4) : δ 1.4-2.53 (8H, m, 4X-CH_2-), 2.53 (1H, br s, -OH), 3.83-4.2 (6H, m, -O-CH_2-CH_2-O-, >CHBr, >CHOH)

Bromohydrin 82

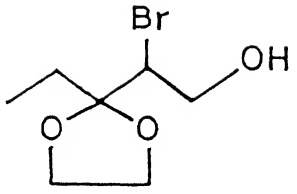


Yield : 87%

IR spectrum (neat) ν_{max} : 3500 (-OH) cm^{-1}

^{1}H NMR spectrum (CCl_4) : δ 0.93-1.07 (3H, two s, -CH_3), 1.17-2.4 (5H, m, 2X-CH_2-, >C<u>H</u>CH_3), 2.57 (1H, br s, -OH), 3.53-4.37 (6H, m, -O-CH_2-CH_2-O-, >CHBr, >C<u>H</u>OH)

Bromohydrin 83

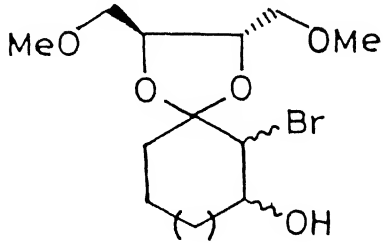


Yield : 83%

IR spectrum (neat) ν_{max} : 3450 (-OH) cm^{-1}

^1H NMR spectrum (CCl_4) : δ 0.9 (3H, t, $-CH_2\underline{CH}_3$, J = 7 Hz), 1.37-2.33 (2H, m, $-\underline{CH}_2CH_3$), 2.9 (1H, s, -OH), 3.67-4.27 (7H, m, $-O-CH_2-CH_2-O-$, $-\underline{CH}_2OH$, >CHBr)

2-Bromo-3-hydroxycyclohexanone cyclic (1S, 2S)-1,2-Bis (methoxymethyl) ethylene acetal 101



Yield : 81%

IR spectrum (CCl_4) ν_{max} : 3450 (-OH) cm^{-1}

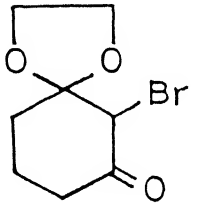
^1H NMR spectrum (CCl_4) : δ 1.4-2.27 (7H, m, 3X-CH_2-, >$\underline{CH}$OH), 3.07-3.6 (11H, m, 2X-CH_2OCH_3, >CHBr), 3.6-4.2 (3H, m, methines, >$\underline{CH}$OH)

General Procedure for the Oxidation of Bromohydrins to α-Bromoketones

To a mixture of dry pyridine (1.58 gm, 20 mmol) in dry

dichloromethane (15 ml) was added CrO_3 (1.0 gm, 10 mmol) and dry celite (1.0 gm). After stirring for 30 minutes at 20-25°C, bromohydrin (1 mmol) in 2 ml of dichloromethane was added to it and stirring was continued for further 40 minutes. Dilution of the reaction mixture with ether (25 ml), filtration through a pad of silica gel and concentration of the filtrate gave the crude product whose purification by preparative TLC [eluent : petroleum ether-ethyl acetate] gave the pure bromoketone.

2-Bromo-3-oxo cyclohexanone ethylene acetal 84



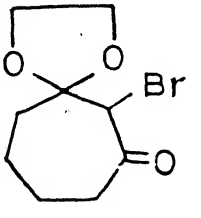
Yield : 65%

m.p. : 65°C

IR spectrum (KBr) ν_{max} : 1720 (C=O) cm^{-1}

^1H NMR spectrum (CCl_4) : δ 1.4-3.3 (6H, m, methylenes), 3.77-4.11 (5H, m, >CHBr, $-O-CH_2-CH_2-O-$)

2-Bromo-3-oxo cycloheptanone ethylene acetal 85

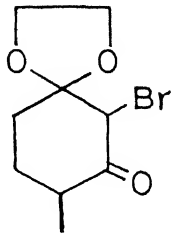


Yield : 78%

IR spectrum (neat) ν_{max} : 1695 (C=O) cm^{-1}

^{1}H NMR spectrum (CCl_4) : δ 1.53-3.17 (8H, m, 4X-CH_2-), 3.73-4.5 (5H, m, -OCH_2-CH_2-O-), -$\overset{|}{C}$HBr).

2-Bromo-4-methyl-3-oxo cyclohexanone ethylene acetal 86

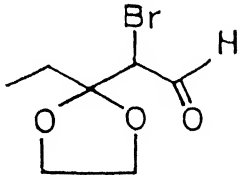


Yield : 80%

IR spectrum (neat) ν_{max} : 1715 (C=O) cm^{-1}

^{1}H NMR spectrum (CCl_4): δ 0.97 (3H, d, >HC$C\underline{H}_3$, J = 7 Hz), 1.07-3.4 (5H, m, 2X-CH_2- and >$C\underline{H}CH_3$), 3.7-4.0 (5H, m, >CHBr, -O-CH_2-CH_2-O).

1-Bromo-1-formyl-butan-2-one ethylene acetal 87

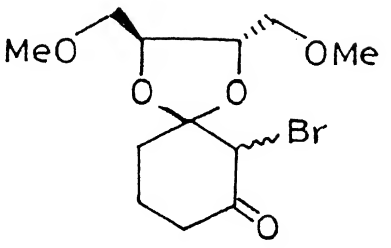


Yield : 80%

IR spectrum (neat) ν_{max} : 1720 (C=O) cm^{-1}

^{1}H NMR spectrum (CCl_4) : δ 0.9 (3H, t, -$CH_2C\underline{H}_3$, J = 7 Hz), 1.47-1.93 (2H, m, -$C\underline{H}_2CH_3$), 3.8-4.33(5H, m, >CHBr, -O-CH_2-CH_2-O-), 9.23 (1H, d, -CHO, J = 7 Hz).

2-Bromo-3-oxo-cyclohexanone cyclic (1S, 2S)-1,2-Bis (methoxy methyl) ethylene acetal 104



Yield : 71%

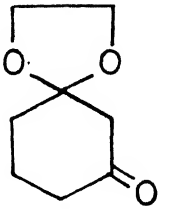
IR spectrum (neat) ν_{max} : 1710 (C=O) cm^{-1}

^1H NMR spectrum (CCl_4) : δ 1.53-2.5 (6H, m, methylenes), 3.37 (6H, s, -OMeX2), 3.47 (4H, d, $MeOC\underline{H}_2$-X2, J = 3 Hz), 3.93-4.4 (3H, m, methines).

General Procedure for n-Bu_3SnH Reduction of Bromoketones

To a solution of a bromoketone (1 mmol) in benzene (10 ml) was added n-Bu_3SnH (2 mmol) and 50-80 mg of AIBN and the reaction mixture was refluxed for 2 hours. Solvent was removed under vacuum and the crude product was purified by column chromatography [eluent : petroleum ether-ethyl acetate] to obtain the pure ketoacetal.

3-oxo-cyclohexanone ethylene acetal 91



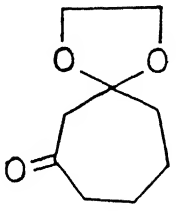
Yield : 81%

IR spectrum (neat) ν_{max} : 1720 (C=O) cm^{-1}

^1H NMR spectrum (CCl_4) : δ 1.6-1.93 (4H, m, 2X-CH_2-), 1.93-2.3 (2H, m, -C(=O)-CH_2-), 2.37 (2H, s, -C(=O)-CH_2-C(O-)(O-)), 3.83 (4H, s, -O-CH_2-CH_2-O-).

Mass spectrum m/z : 156 (M^+)

3-Oxo-cycloheptanone ethylene acetal 92



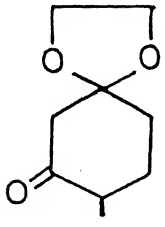
Yield : 88%

IR spectrum (neat) ν_{max} : 1710 (C=O) cm^{-1}

^1H NMR spectrum (CCl_4) : δ 1.53-2.0 (6H, m, 3X-CH_2-), 2.13-2.53 (2H, m, -C(=O)-CH_2-), 2.67 (2H, s, -C(=O)-CH_2-C(O-)(O-)), 3.83 (4H, s, -O-CH_2-CH_2-O-).

Mass spectrum m/z : 170 (M^+)

3-Oxo-4-methyl-cyclohexanone ethylene acetal 93



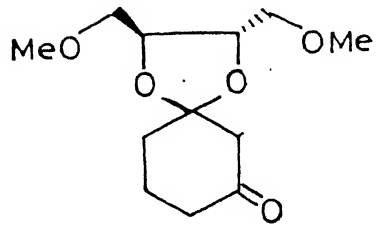
Yield : 85%

IR spectrum (neat) ν_{max} : 1710 (C=O) cm^{-1}

^{1}H NMR (CCl_4) : δ 0.97 (3H, d, >CH-C<u>H</u>$_3$), 1.13-2.9 (5H, m, -C<u>H</u>CH$_3$, 2X-CH$_2$-), 2.47 (2H, s, -C(=O)-CH$_2$-C(O-)(O-)-), 3.87 (4H, m, -O-CH$_2$-CH$_2$-O-).

Mass spectrum m/z : 170 (M^+)

3-Oxo-cyclohexanone cyclic (1S, 2S)-1,2-Bis (methoxymethyl) ethylene acetal <u>106</u>



Yield : 78%

IR spectrum (neat) ν_{max} : 1720 (C=O) cm^{-1}

^{1}H NMR (CCl_4) : δ 1.63-2.43 (6H, m, 3X-CH$_2$-, 2.65 (2H, s, -C(=O)-CH$_2$-C(O-)(O-)-), 3.44 (6H, s, 2X-OMe), 3.5 (4H, d, 2X-C<u>H</u>$_2$-OMe, J = 3.75 Hz), 3.97-4.16 (2H, m, 2 methines).

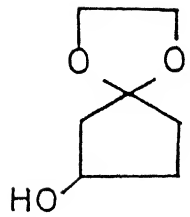
Mass spectrum m/z : 249 (M^+)

Anal. Calcd. for $C_{12}H_{20}O_5$: C, 59.01; H, 8.20

Found : C, 59.2; H, 8.25%

Preparation of 3-hydroxy cyclopentanone ethylene acetal <u>88</u>

To a solution of <u>79</u> (1 mmol) in benzene (5 ml) was added n-Bu_3SnH (580 mg, 2 mmol) and AIBN (50 mg). The reaction mixture was then heated under reflux for 2 hours. Solvent was removed under vacuum and the residue chromatographed [petroleum ether-ethyl acetate (92:8)] to obtain pure <u>88</u> (110 mg)

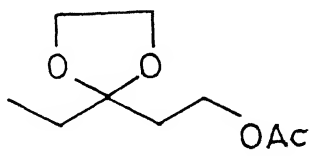


Yield : 76%

IR spectrum (neat) ν_{max} : 3400 (-OH) cm^{-1}

^1H NMR (CCl_4) : δ 1.9-2.3 (6H, m, 3X-CH_2-), 3.77 (4H, s, -O-CH_2-CH_2-O-), 3.9-4.57 (2H, m, -$\overset{|}{C}$HOH).

Preparation of 1-acetyl-3-pentanone ethylene acetal 90



Bromohydrin 83 (1 gm, 4.44 mmol), n-Bu_3SnH (2 gm, 6.87 mmol) and AIBN (100 mg) were mixed in benzene (10 ml) and refluxed for 4 hours. Solvent was removed under vacuum and the crude product was purified by column chromatography [eluent : petroleum ether-ethyl acetate (80:20)] to obtain 89 in 89% yield.

For characterisation purpose, 0.1 gm (0.44 mmol) of pure bromohydrin was acetylated by treating with acetic anhydride (170 mg, 1.7 mmol), pyridine (0.5 ml) and a catalytic amount of 4-(dimethylamino)pyridine (10 mg) and stirred at room temperature for 10 hour. After the reaction was complete, the reaction mixture was washed with water and extracted with CH_2Cl_2 (3x10 ml). Drying over anhydrous sodium sulphate and evaporation of the solvent gave the crude product whose purification by column chromatography [eluent : ethyl acetate - petroleum ether (5:95)] gave the acetate 90 (90 mg).

Yield : 77%

IR spectrum (neat) ν_{max} : 1720 (C=O) cm^{-1}

^1H NMR (CCl_4) : δ 0.87 (3H, t, $-CH_2\underline{CH_3}$, J = 7 Hz), 1.07-1.87 (4H, m, $2X-\underline{CH_2}-$), 1.93 (3H, s, $-\overset{O}{\overset{\|}{C}}-CH_3$), 3.8 (4H, s, $-O-\underline{CH_2}-\underline{CH_2}-O-$), 3.97 (2H, t, $-\underline{CH_2}OAc$, J = 7 Hz).

Mass spectrum m/z : 188 (M^+)

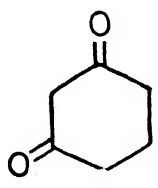
Anal. Calcd. for $C_9H_{16}O_4$: C, 57.45; H, 8.51

Found : C, 57.13; H, 8.73%

General Procedure for the hydrolysis of 3-keto acetals :

To a suspension of silica gel (100-200 mesh, 500 mg) in CH_2Cl_2 (3 ml) was added 15% H_2SO_4 (0.15 ml). The mixture was stirred at room temperature until the turbidity in the dichloromethane layer had disappeared. A solution of keto acetal (1 mmol) in 1 ml of dichloromethane was added to it and the reaction mixture was stirred at room temperature for 20 hours (for 50 hours in the case of 1,3-cycloheptanedione mono ethylene acetal). It was neutralized with sodium bicarbonate, filtered and the solid residue washed with dichloromethane. The filtrate was concentrated and the crude dione purified by short column or by vacuum distillation.

1,3-cyclohexane dione <u>95</u>



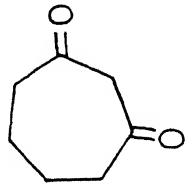
Yield : 70%

m.p. :102^{o}C [Lit.[42] m.p. : 105-106^{o}C]

IR spectrum (neat) ν_{max} : 1715 (weak C=O; keto form), 1608 (C=O, C=C; enol form) cm^{-1}

^{1}H NMR spectrum (DMSO-d_6) : δ 1.5-2.5 (6H, m, 3X-CH_2-), 5.21 (1H, s, =CH-), 11.3 (1H, br s, -OH)

1,3-cycloheptane dione 96

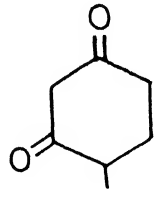


Yield : 71%

IR spectrum (CCl_4) ν_{max} : 1728 and 1705 (twin C=O) cm^{-1}.

^{1}H NMR spectrum ($CDCl_3$) : δ 1.4-2.2 (4H, m, 2X-CH_2-), 2.3-2.6 (4H, m, 2X-CH_2-C(=O)-), 3.5 (2H, s, -C(=O)-CH_2-C(=O)-)

4-Methyl cyclohexane-1,3-dione 97



Yield : 78%

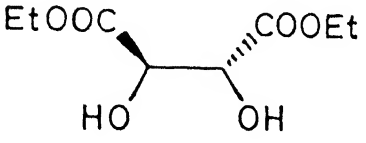
IR spectrum (neat) ν_{max} : 1710 (weak C=O; keto form), 1605 (C=O, C=C; enol form) cm^{-1}.

^{1}H NMR spectrum (DMSO-d_6) : δ 1.03 (3H, d, C_4-CH_3, J = 6 Hz),

1.5-2.8 (5H, m, 2X-CH_2-, -CH), 5.25 (1H, s, =CH-), 10.5 (1H, br s, -OH).

Preparation of chiral diol 121

(i) Preparation of Diethyl Tartrate 118

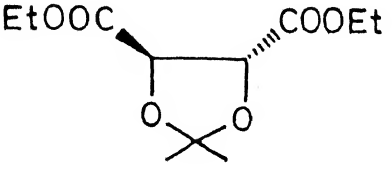


Tartaric acid (10 gms, 66.6 mmol), ethyl alcohol (25 mol), benzene (50 ml) and p-toluenesulfonic acid (1 gm) were mixed and heated at 80°C with azeotropic removal of water for 10 hours. Neutralisation of the reaction mixture with a saturated solution of sodium bicarbonate follwed by the usual workup with ethyl acetate gave the crude product which was purified by vacuum distillation.

Yield : 90%

b.p. : 110°C/0.01 mm [Lit. 124°C/0.02 mm]

(ii) Isopropylidation of Diethyl tartrate 119



Diethyl tartrate (10 gms, 48.5 mmol), 2,2-dimethoxy propane (10.08 gm, 97 mmol) and p-toluenesulfonic acid (0.834 gm, 4.85 mmol) were mixed in dry benzene (30 ml) and heated at 80°C for 12 hours. During this period benzene-methanol azeotrope was removed

slowly at 58°C. At the end of the reaction, a saturated solution of sodium bicarbonate was added to the reaction mixture and it was diluted (15 ml) with 50 ml of water. This was thoroughly extracted with ether (3x50 ml) and the combined ethereal layer was washed with brine (25 ml) and dried over anhydrous sodium sulphate. Ether was removed under reduced pressure and the crude product was purified by vacuum distillation.

b.p. : 110-115°C/0.05 mm [Lit. b.p. : 82-90°C/0.02 mm]

$[\alpha]_D^{25} = -49^\circ$ [Lit. $[\alpha]_D^{20} = -53.1^\circ$

IR spectrum (neat) ν_{max} : 1750 (-C=O) cm^{-1}

^1H NMR (CCl_4) : δ 1.4 (6H, s, 2X-CH_3), 3.75 (6H, s, 2X-OCH_3), 4.6 (2H, s, -C(=O)-CH-CH-C(=O)-).

(iii) Preparation of 2,3-o-isopropylidine-L-threitol 120

To a suspension of $LiAlH_4$ (9.2 gms, 110 mmol) in anhydrous THF (40 ml) was added dropwise a solution of diethyl-o-isopropylidene-L-tartrate 119 (12 gm, 50 mmol) in 30 ml of THF over a period of 2 hours with external cooling by means of an ice-water bath. The mixture was then refluxed for 10 hours. The reduction complex was decomposed very carefully by successive addition of ethyl acetate (10 mmol) and 5 ml of water. The inorganic precipitate was removed by filtration and thoroughly extracted with ethyl acetate. The combined ethyl acetate extract was dried over anhydrous sodium sulphate and concentrated. The crude product was purified by vacuum distillation to afford the diol 120.

Yield : 7.0 gm (86%)

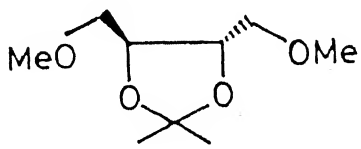
b.p. : 115-120°C/0.1-0.2 mm [Lit. b.p. : 91-93°C/0.01-0.02 mm]

$[\alpha]_D^{25}$ = +3.6° (C_5, $CHCl_3$) [Lit. $[\alpha]_D^{25}$ = +4.1° (C_5, $CHCl_3$)

IR spectrum (neat) ν_{max} : 3400 (br, -OH) cm^{-1}

^1H NMR ($CDCl_3$) : δ 1.43 (6H, s, gem 2X-CH_3), 3.2 (2H, s, 2X-OH), 3.5-3.8 (4H, m, 2X-$C\underline{H}_2OH$), 3.9-4.1 (2H, m, methines).

(iv) Preparation of 2,3-O-isopropylidine-L-threitol dimethyl ether 120A



To a well stirred suspension of powdered anhydrous KOH (5.38 gm, 96 mmol) in dry DMSO (20 ml) was slowly added a solution of 120 (6.48 gms, 40 mmol) in 5 ml of DMSO at 10-15°C. After stirring for 1 hour, MeI (13.63 gm, 96 mmol) was slowly added to it and stirring was continued at 20°C for further 4 hours. The reaction mixture was then poured into 25 ml of ice-cold water and extracted with ether (4x25 ml). The combined ethereal extract was washed with water (2x10 ml) followed by brine (10 ml). Drying over anhydrous sodium sulphate followed by evaporation of ether gave a crude product which was purified by Kugelrohr distillation to obtain the dimethyl ether 120A

Yield : 5.3 gm, 70%

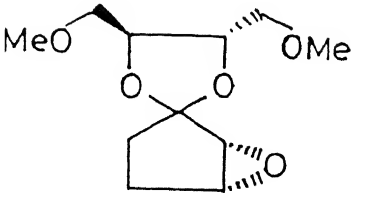
b.p. : 95°C/10 mm [Lit. b.p. : 89-92°C/12 mm)

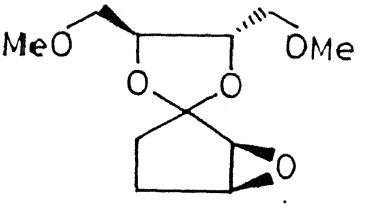
$[\alpha]_D^{25}$ = -8° (C, 0.5, $CHCl_3$)

$[\alpha]_D^{19}$ = for its enantiomer +8.9° (C, 0.29, $CHCl_3$)

IR spectrum (neat) ν_{max} : 1170, 1140, 1080, 1050 (C-O-C) cm^{-1}

Preparation of 2,3-epoxy acetal 102 (A and B)





Compound 98 (856 mg, 4 mmol) was treated with water (0.30 ml, 10 mmol) in DMSO (4 ml) and the reaction mixture was cooled to about 10°C with stirring. N-bromosuccinimide (890 mg, 5 mmol) was added in portions. The stirring was continued for further 30 minutes at 10°C. A yellow colour developed which deepened as the reaction progressed. The reaction mixture was then quenched with dilute aqueous sodium bicarbonate solution (10 ml) with concomitant discharge of the yellow colour, followed by extraction of the product into ether (4x20 ml). The combined ethereal layer was washed with cold water (10 ml) and brine (10 ml) and dried over anhydrous sodium sulphate. Removal of the solvent gave a crude product which was purified by column chromatography [eluent: 20% EA+PE] to afford the bromohydrin 100 (1.0 gm).

Yield : 81%

The bromohydrin 100 (0.558 gm, 1.8 mmol) in 1 ml of dry THF was added dropwise to a stirring suspension of sodium hydride (0.095 gm, 3.96 mmol) in 3 ml of THF at 0°C and the reaction mixture was brought to 40°C during a period of 4 hours. THF was removed under vacuum and ice-cold water (5 ml) was added to the mixture followed by extraction of the product into ether (4x20 ml). The combined ethereal layer was washed with brine (10 ml), dried over anhydrous sodium sulphate, filtered and concentrated. The crude product was

purified by column chromatography [eluent : petroleum ether-ethyl acetate (93:7)].

Yield : 70%

IR spectrum (neat) ν_{max} : 1240, 850 (C-O-C oxirane) cm^{-1}

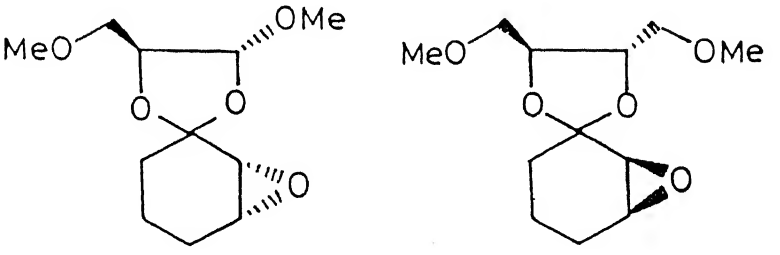
^1H NMR spectrum (CCl_4) : δ 1.4-2.1 (4H, m, 2X-CH_2-), 3.07, 3.17 (1H, two doublets with J = 3 Hz in each case, C_2-H), 3.7-3.27 (11H, m, containing a 6H, s at δ 3.4, 2X-CH_2OCH_3 and $C_3\underline{H}$), 3.85-4.15 (2H, m, methines).

Mass spectrum m/z : 230 (M^+)

Anal. Calcd. for $C_{11}H_{18}O_5$: C, 57.38; H, 7.88

Found : C, 57.61; H, 7.85%.

Preparation of 2,3-epoxy acetal 103



A mixture of 99 (456 mg, 2 mmol) and 80% m-CPBA (518 mg, 2.4 mmol) in dry dichloromethane (5 ml) was refluxed for 2 hours. After cooling, major amount of m-CPBA was removed by filtration. The filtrate was diluted with 25 ml of dichloromethane and shaken successively with saturated Na_2SO_3 and 10% NaOH solution. It was washed with water (2x5 ml) and brine (15 ml). Drying over anhydrous sodium sulphate and evaporation of dichloromethane gave the crude product which was purified by column chromatography [eluent : petroleum ether-ether (60:40)] to afford 103.

Yield : 380 mg, 78%

IR spectrum (neat) ν_{max} : 1260, 870 (C-O-C, oxirane) cm^{-1}.

^1H NMR spectrum (CCl_4) : δ 1.37-2.0 (6H, m, 3X-CH_2-), 3.02, 3.12

(1H, two doublets with J = 3 Hz), 3.2-3.7 (11H, m, containing a 6H, s at δ 3.4, 2X-CH_2OCH_3 and $C_3\underline{H}$), 3.93-4.18 (2H, m, methines).

Mass spectrum m/z : 249 (M^+)

Anal. Calcd. for $C_{12}H_{20}O_5$: C, 59.0; H, 8.25

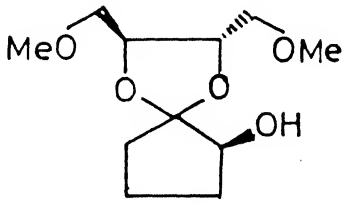
Found : C, 59.2; H, 8.11%.

General procedure for the reduction of 2,3-epoxy acetals by $LiAlH_4$

To a slurry of $LiAlH_4$ (100 mg, 2.6 mmol) in dry THF (4 ml) was slowly added a solution of 2,3-epoxy acetal (2 mmol) in 1 ml of dry THF and the reaction mixture was refluxed for 8 hours. After cooling, the reduction complex was decomposed by successive addition of ethyl acetate (2 ml) and water (1 ml). It was stirred over anhydrous sodium sulphate and then filtered through a sintered funnel. The solid residue was washed with ethyl acetate (25 ml) and the filtrate was concentrated to get the crude product which was purified by column chromatography. Yields and properties of the alcoholic products were as follows :

2-Hydroxycyclopentanone cyclic (1S, 2S)-1,2-Bis(methoxymethyl) ethylene acetal 108

Less polar :



Yield : 40%

^1H NMR spectrum (60 MHz, CCl_4) : δ 1.37-2.03 (6H, m, 3X-CH_2-), 2.5 (1H, br s, -OH), 3.2-3.7 (10H, m, with splitting of the -OCH_3

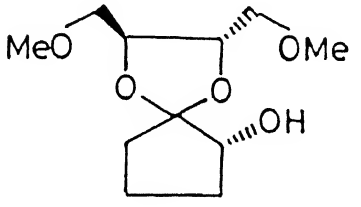
signal), 3.73-4.3 (3H, m, methines, -CHOH).

Mass spectrum m/z : 232 (M^+).

Anal. Calcd. for $C_{11}H_{20}O_5$: C, 56.88; H, 8.68

Found : C, 56.7; H, 8.66%.

More polar :



Yield : 40%

IR spectrum (neat) ν_{max} : 3450 (br, -OH) cm^{-1}.

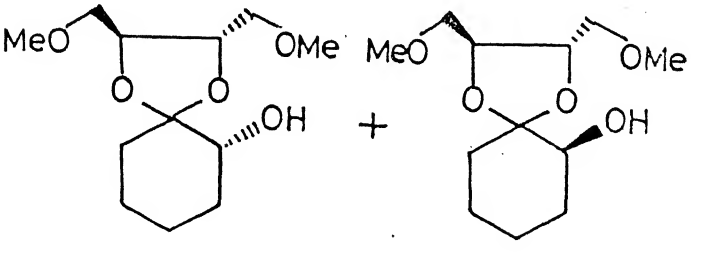
^1H NMR spectrum (CCl_4) : δ 1.37-2.1 (6H, m, 3X-CH_2-), 2.5 (1H, br s, -OH), 3.3-3.7 (10H, m, with a singlet at δ 3.4, 2X(-CH_2OCH_3), 3.8-4.3 (3H, m, >CHOH, methines).

Mass spectrum m/z : 232 (M^+)

Anal. Calcd. for $C_{11}H_{20}O_5$: C, 56.88; H, 8.68

Found : C, 57.0; H, 8.8%.

2-Hydroxy cyclohexanone cyclic (1S, 2S)-1,2-Bis (methoxy methyl) ethylene acetal 112



Yield : 79%

IR spectrum (neat) ν_{max} : 3400 (br, -OH) cm^{-1}.

^1H NMR spectrum (CCl_4) : δ 1.2-2.0 (8H, m, 4X-CH_2-), 2.77 (1H, br s, -OH), 3.25-3.67 (10H, m, with splitting of the -OCH_3 signal, 2X-CH_2OCH_3), 3.8-4.33 (3H, m, >CHOH, methines).

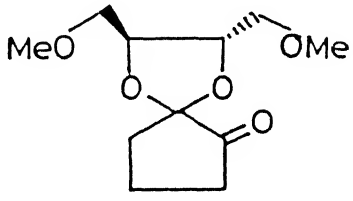
Mass spectrum m/z : 246 (M^+)

Anal. Calcd. for $C_{12}H_{22}O_5$: C, 58.51; H, 9.0

Found : C, 58.5; H, 8.88%.

General procedure for oxidation of 2-hydroxy acetals to 2-keto acetals

2-Oxo-cyclopentanone cyclic (1S, 2S)-1,2-Bis (methoxymethyl) ethylene acetal 105



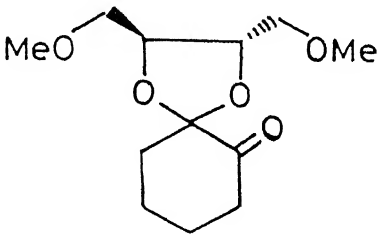
Yield : 74%

IR spectrum (neat) ν_{max} : 1750 cm^{-1}

^1H NMR spectrum (CCl_4) : δ 1.6-2.4 (6H, m, 3X-CH_2-), 3.3-3.67 (10H, m, containing a singlet at δ 3.5, 2X-CH_2OCH_3), 3.8-4.05 (2H, m, methines).

Mass spectrum m/z : 230 (M^+)

2-Oxo-cyclohexanone cyclic (1S, 2S)-1,2-Bis (methoxymethyl) ethylene acetal 107



Yield : 78%

IR spectrum (neat) ν_{max} : 1710 cm^{-1}.

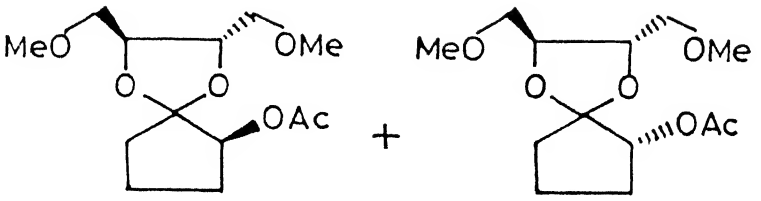
^1H NMR spectrum (CCl_4) : δ 1.5-2.63 (8H, m, 4X-CH_2-), 3.3-3.65 (10H, m, 2X-CH_2OCH_3), 3.83-4.1 (2H, m, methines).

Mass spectrum m/z : 244 (M^+)

General Procedure for the reduction of 2-keto acetals to 2-hydroxy acetals with $LiAlH_4$

To an ethereal solution of $LiAlH_4$ (18 mg, 0.5 mmol) at -78°C was added a solution of 2-keto acetal (1 mmol) in ether (5 ml). After stirring the reaction mixture for 4 hours, it was quenched with water and extracted with ether. Drying over sodium sulphate and removal of the solvent gave almost pure hydroxy acetal. A portion of this alcohol (0.33 mmol) was dissolved in dry dichloromethane (2 ml) and treated with acetic anhydride (100 mg, 1 mmol), pyridine (79 mg, 1 mmol) and 4-(dimethylamino) pyridine (5 mg). The reaction mixture was then stirred at room temperature for 15 hours. Usual workup gave the crude product which was purified by column chromatography [eluent : petroleum ether-ethyl acetate] to obtain the pure product.

2-Acetoxy cyclopentanone cyclic (1S, 2S)-1,2-Bis (methoxymethyl) ethylene acetal 109



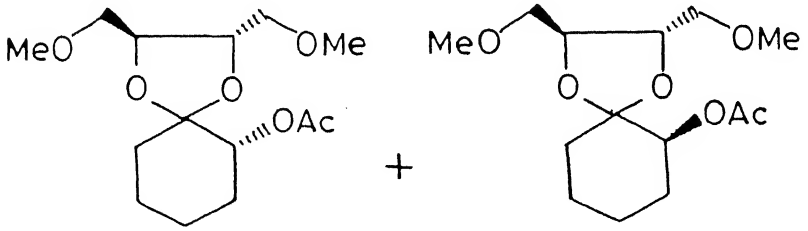
Yield : 79%

IR spectrum (neat) ν_{max} : 1730 cm^{-1}.

^1H NMR spectrum (CCl_4) : δ 1.4-1.9 (6H, m, methylenes), 2.0 (3H, s, $-OCOCH_3$), 3.23-3.5 (10H, m, containing a singlet at δ 3.27, $-CH_2OCH_3$X2), 3.67-3.9 (2H, m, methines), 4.57-4.89 (1H, m, $-\underline{C}\underline{H}OAc$).

Mass spectrum m/z : 274 (M^+)

2-Acetoxy cyclohexanone cyclic (1S, 2S)-1,2-Bis (methoxymethyl) ethylene acetal 113



Yield : 82%

IR spectrum (neat) ν_{max} : 1725 cm^{-1}.

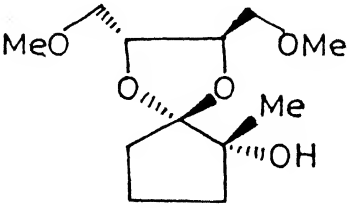
^1H NMR spectrum (CCl_4) : δ 1.13-1.87 (8H, m, methylenes), 1.93 (3H, s, $-OCOCH_3$), 3.23-3.47 (10H, m, 2X $-CH_2OMe$), 3.6-4.0 (2H, m, methines), 4.47-4.83 (1H, m, $-\underline{C}\underline{H}OAc$).

Mass spectrum m/z : 288 (M^+)

General Procedure for the Addition of MeMgI to 2-keto acetals

To a suspension of clean and dry magnesium turnings (29 mg) in anhydrous ether (0.5 ml) under nitrogen atmosphere (containing a small crystal of iodine) was added methyl iodide (175 mg, 1.23 mmol) in 0.5 ml of ether at room temperature. After all the magnesium had reacted, the reaction mixture was cooled to 0^oC and a solution of 2-keto acetal (1 mmol) in 1 ml of ether was added to it. The reaction mixture was brought to room temperature during a period of 1 hour, and stirred for further 2 hours. Saturated aqueous ammonium chloride solution (5 ml) was slowly added to it and stirring was continued for 10 minutes. Extraction with ether (3x15 ml), washing with brine (5 ml), drying over anhydrous sodium sulphate followed by removal of the solvent gave the crude product whose purification by column chromatography gave the pure hydroxy compound.

2-Hydroxy-2-methyl cyclopentanone cyclic (1S, 2S)-1,2-Bis (methoxy methyl) ethylene acetal 114



Yield : 60%

IR spectrum (neat) ν_{max} : 3450 cm^{-1}.

^1H NMR spectrum (CCl_4) : δ 1.1 (3H, s, $-CH_3$), 1.4-1.83 (6H, m,

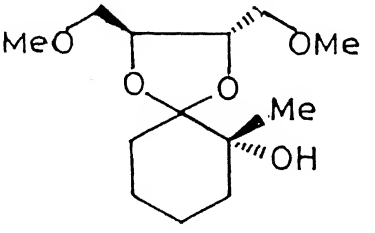
methylenes), 1.97 (1H, br s, -OH), 3.1-3.7 (10H, m, contains a singlet at δ 3.27 (2X-CH_2OCH_3)), 3.8-4.0 (2H, m, methines).

Mass spectrum m/z : 246 (M^+)

Anal. Calcd. for $C_{12}H_{22}O_5$: C, 58.51; H, 9.01

Found : C, 58.42; H, 9.1%.

2-Hydroxy - 2-methyl cyclohexanone cyclic (1S, 2S)-1,2-Bis (methoxy methyl) ethylene acetal 116



Yield : 80%

IR spectrum (neat) ν_{max} : 3425 cm^{-1}.

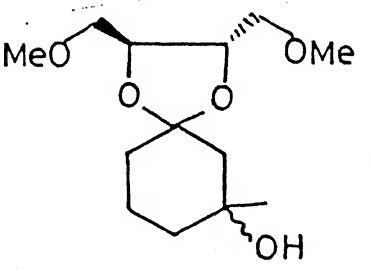
^1H NMR spectrum (CCl_4) : δ 1.07 (3H, s, -CH_3), 1.23-1.67 (8H, m, methylenes), 1.8 (1H, br s, -OH), 3.6-3.17 (10H, m, containing a singlet at δ 3.27 (2X-CH_2OCH_3), 3.73-4.0 (2H, m, methines).

Mass spectrum m/z : 260 (M^+)

Anal. Calcd. for $C_{13}H_{24}O_5$: C, 59.98; H, 9.29

Found : C, 60.2; H, 9.41%.

3-Hydroxy - 3-methyl cyclohexanone cyclic (1S, 2S)-1,2-Bis (methoxy methyl) ethylene acetal 115



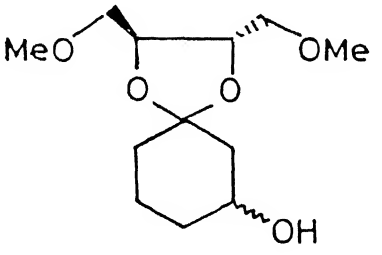
Yield : 72%

IR spectrum (neat) ν_{max} : 3450 cm^{-1}.

^1H NMR spectrum (CCl_4) : δ 1.13-1.27 (3H, 2s, >CH-C<u>H</u>$_3$), 1.6-2.07 (8H, m, methylenes), 2.3 (1H, br s, -OH), 3.6-3.27 (10H, m, containing a singlet at δ 3.4, -CH_2OCH_3-2X), 3.93 (2H, m, methines).

Mass spectrum m/z : 260 (M^+)

3-Hydroxy cyclohexanone cyclic (1S, 2S)-1,2-Bis (methoxymethyl) ethylene acetal <u>110</u>

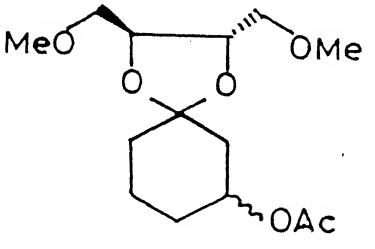


Yield : 82%

IR spectrum (neat) ν_{max} : 3450 cm^{-1}.

^1H NMR spectrum (CCl_4) : δ 1.1-1.94 (6H, s, methylenes), 2.93 (1H, br s, -OH), 3.27 (6H, s, -OMeX2), 3.4 (4H, d, J = 3 Hz, -C<u>H</u>$_2$OMeX2), 3.53-3.93 (3H, m, methines).

3-Acetoxy cyclohexanone cyclic (1S, 2S)-1,2-Bis (methoxymethyl) ethylene acetal <u>111</u>



Yield : 82%

IR spectrum (neat) ν_{max} : 1720 cm^{-1}.

^1H NMR spectrum (CCl_4) : δ 1.26-2.06 (8H, m, methylenes), 1.93

(3H, s, -$OCOCH_3$), 3.4 (10H, br s, -CH_2OCH_3-X2), 3.83 (2H, m, methines), 4.67 (1H, m, -C<u>H</u>OAc).

Mass spectrum m/z : 208 (M^+)

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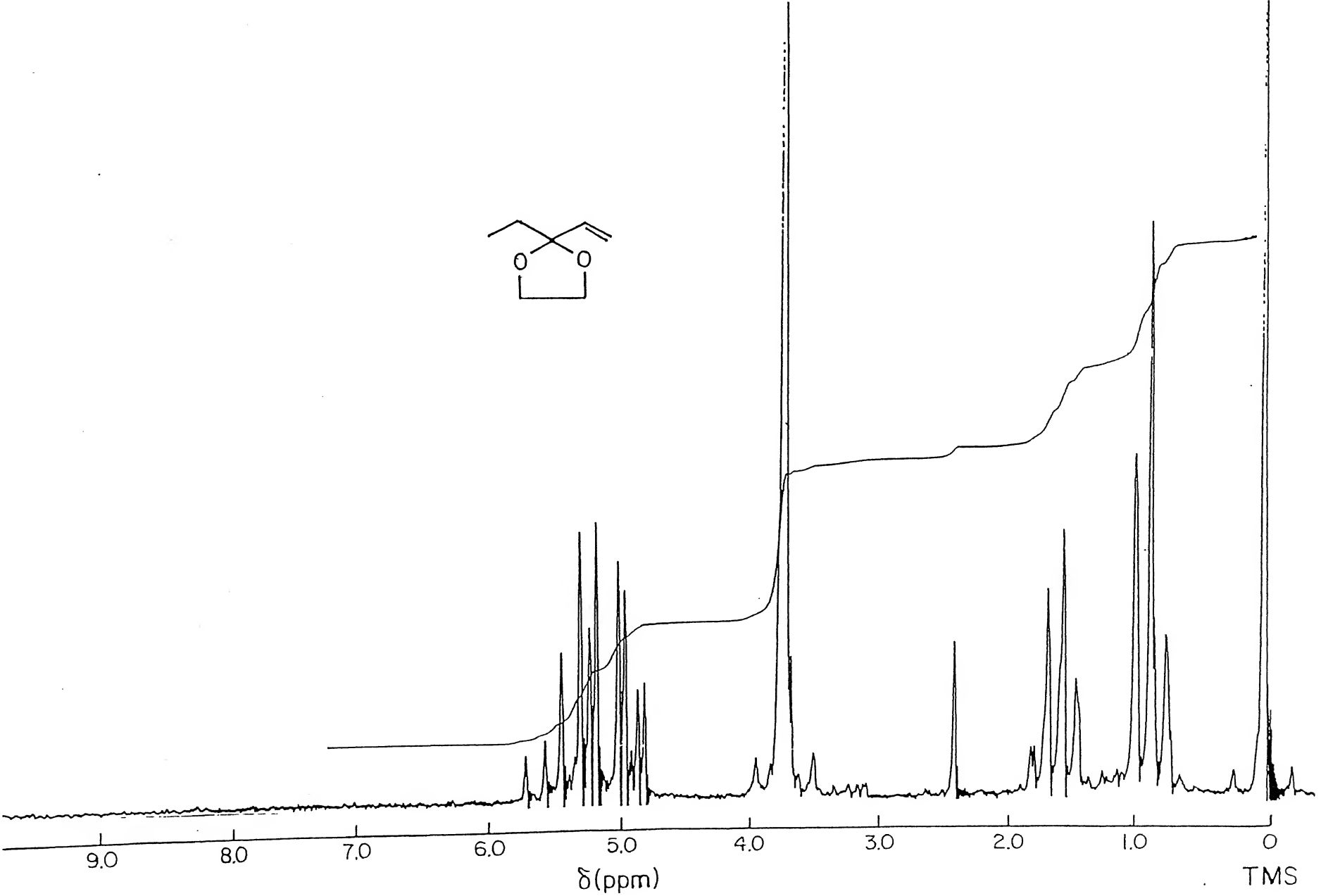
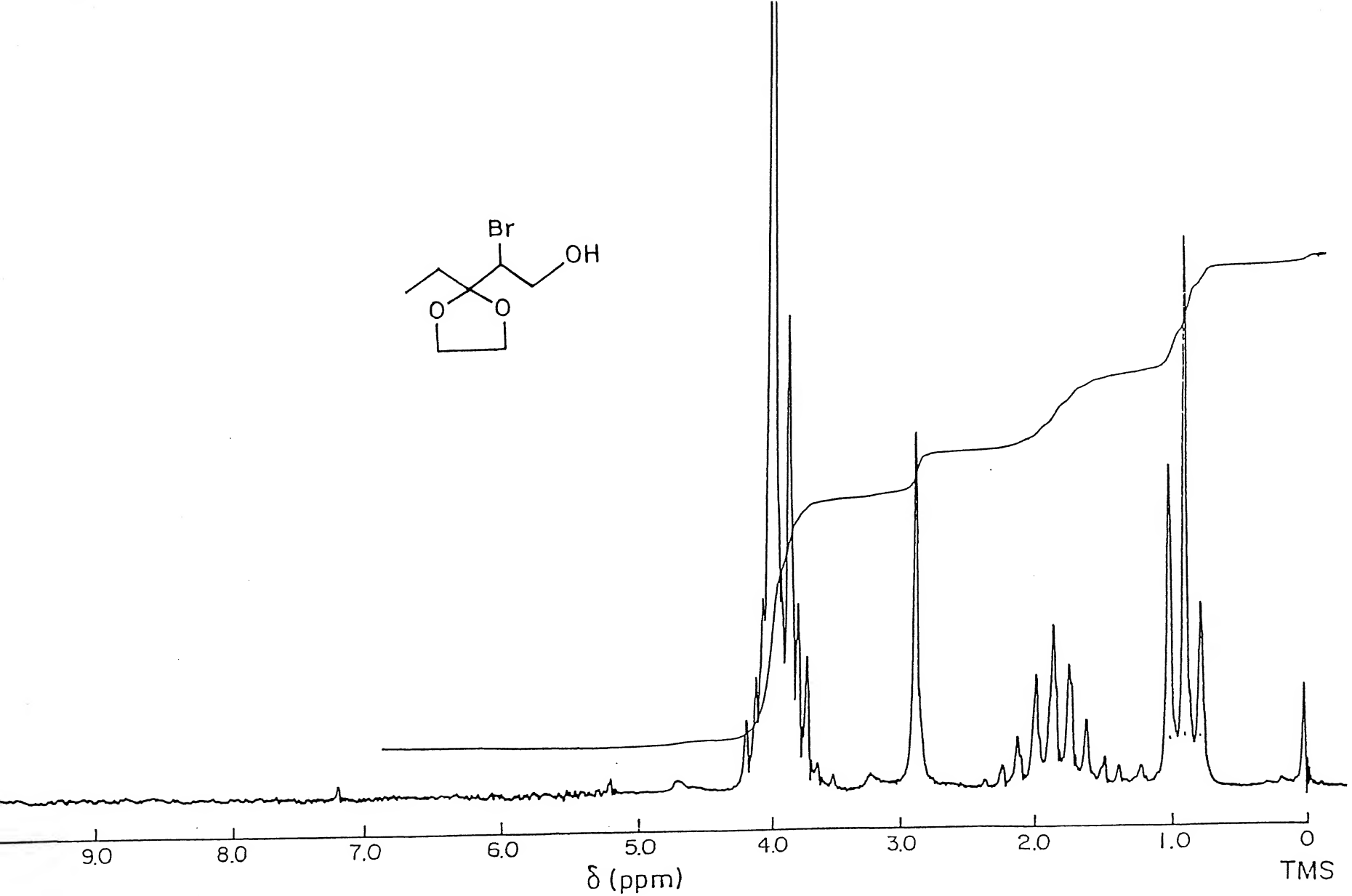
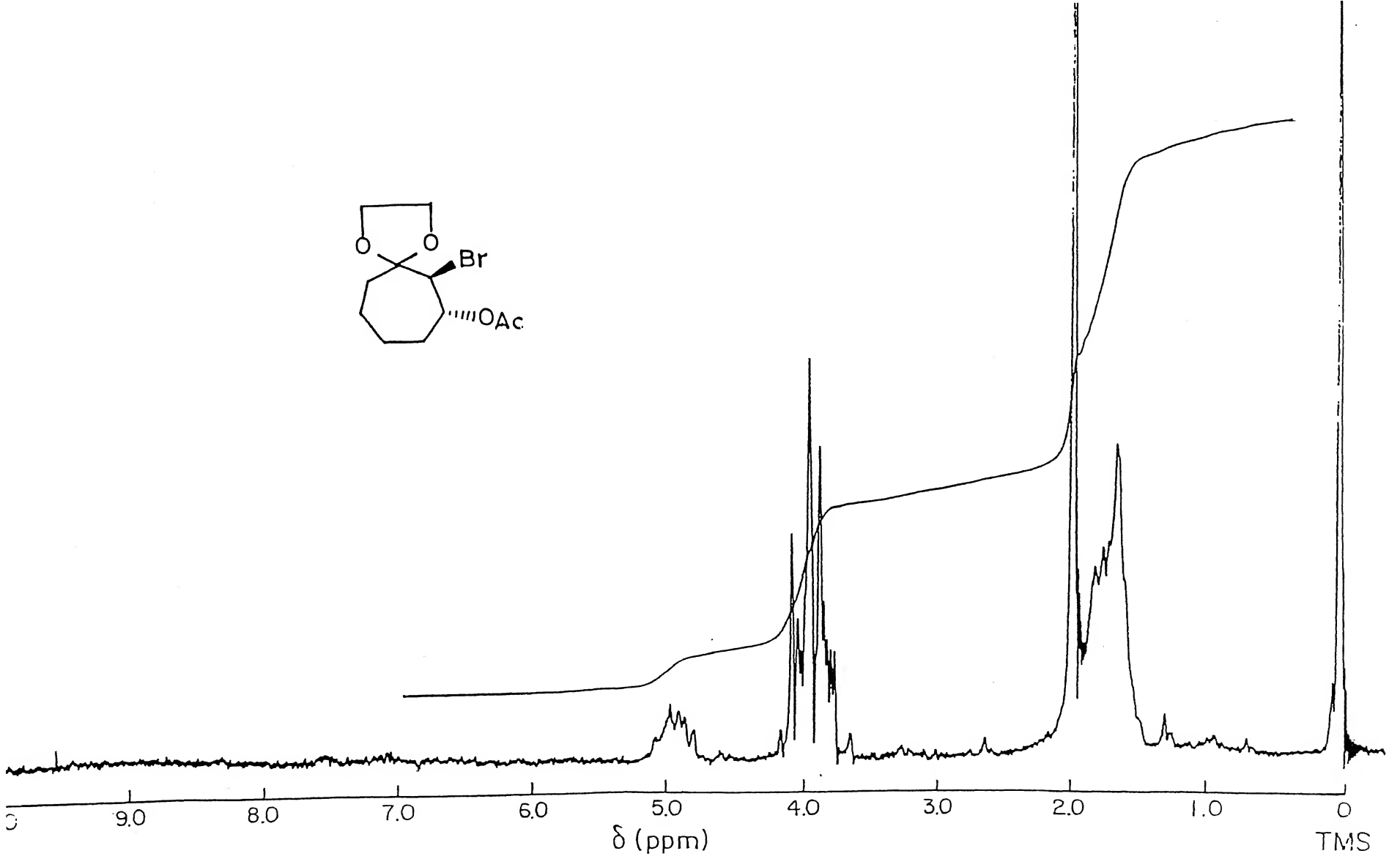


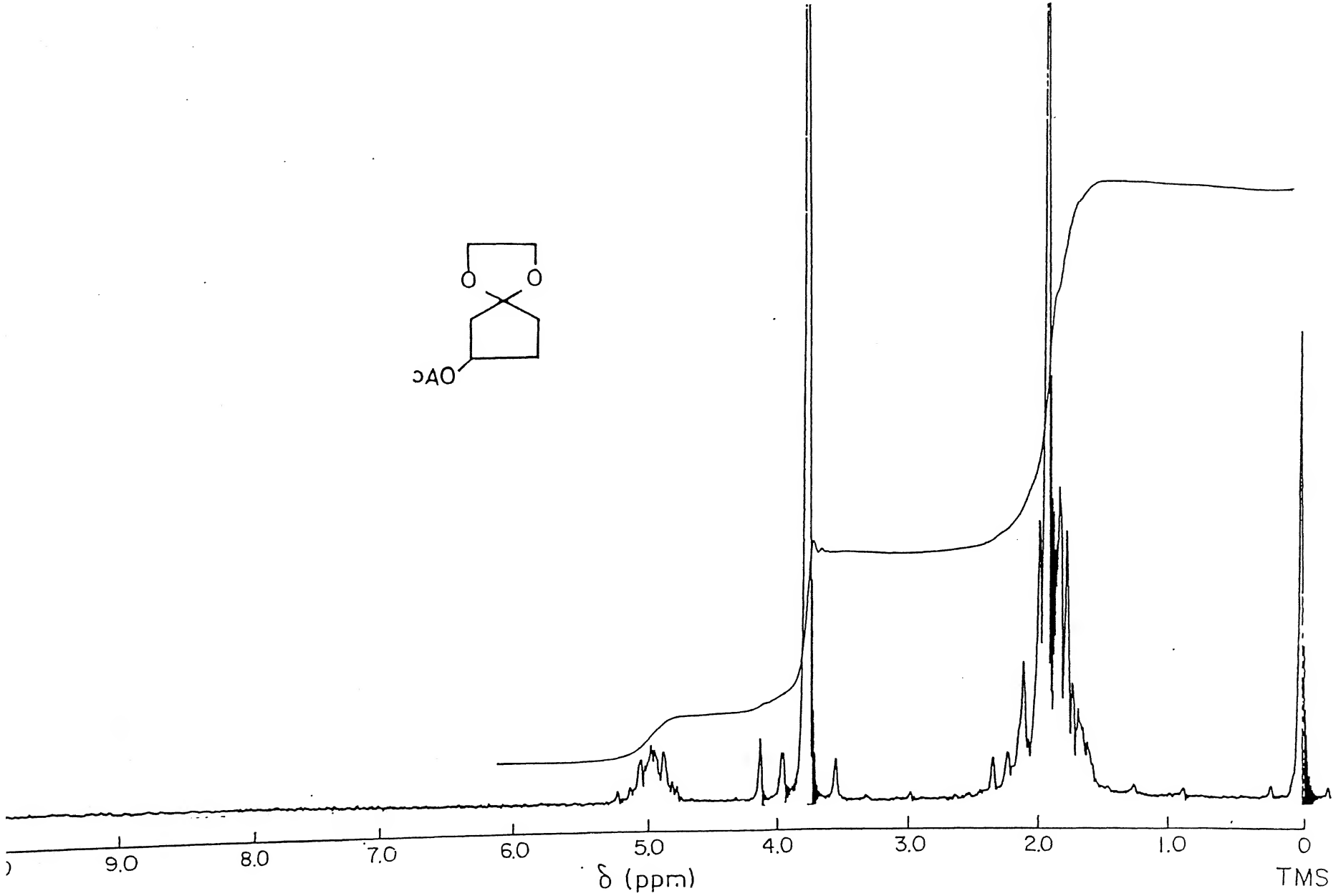
60 MHz ^{1}H NMR spectrum of the compound 78



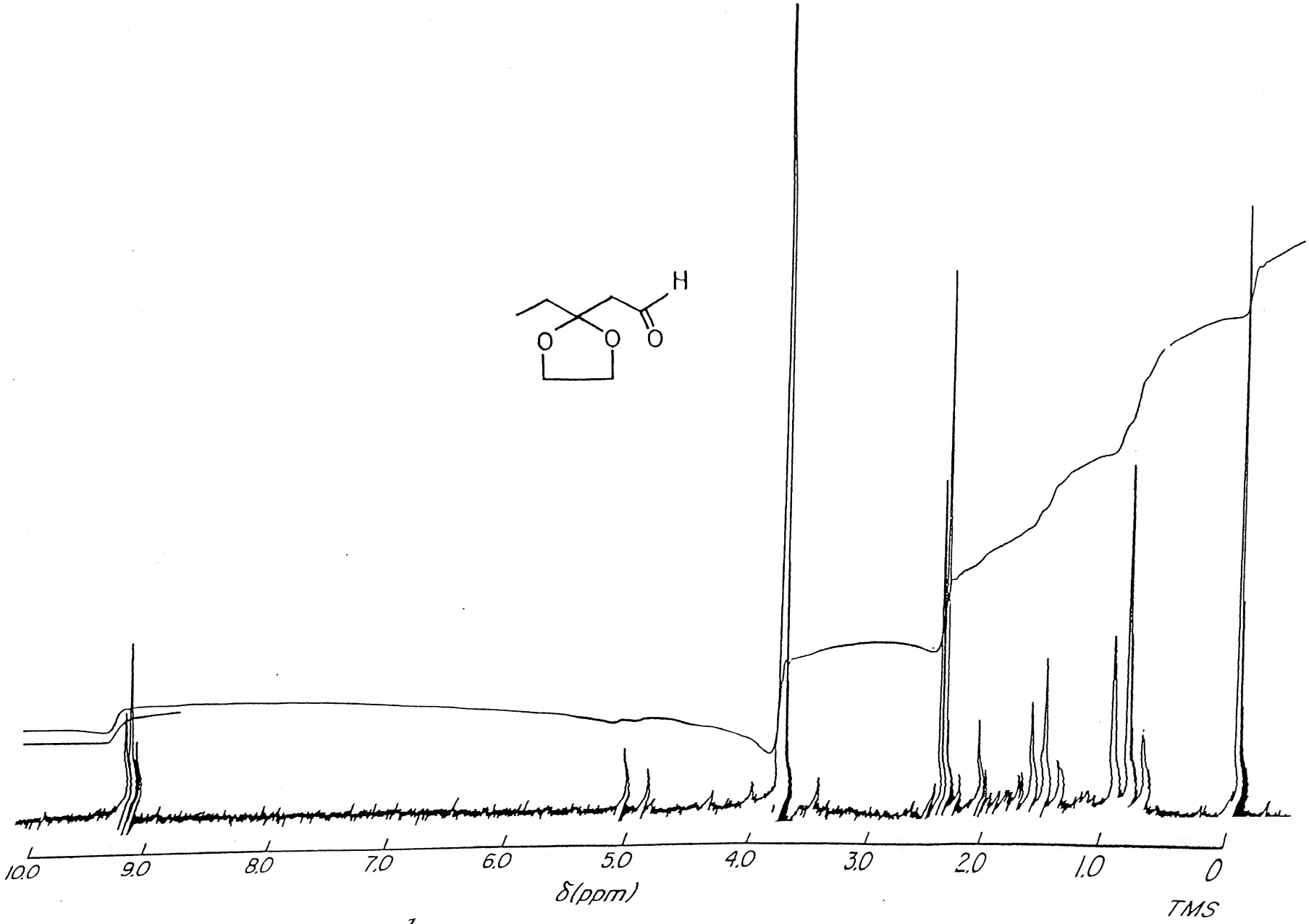
60 MHz ^{1}H NMR spectrum of the compound 83



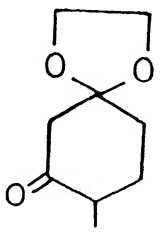
^{1}H NMR spectrum of the compound 81



60 MHz ^{1}H NMR spectrum of the compound 88



60 MHz ^{1}H NMR spectrum of the compound 94

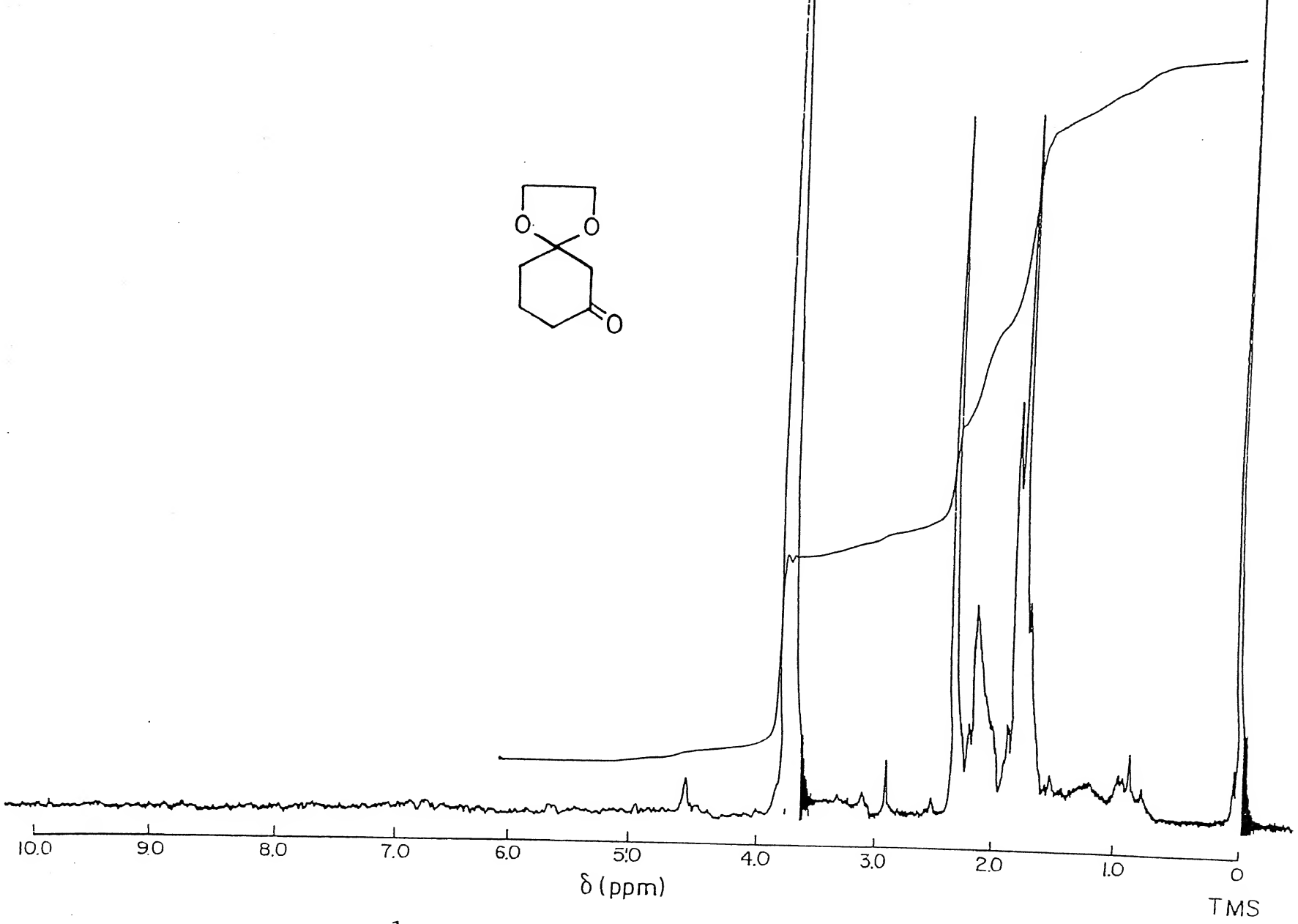


10.0 9.0 8.0 7.0 6.0 5.0 4.0 3.0 2.0 1.0 0

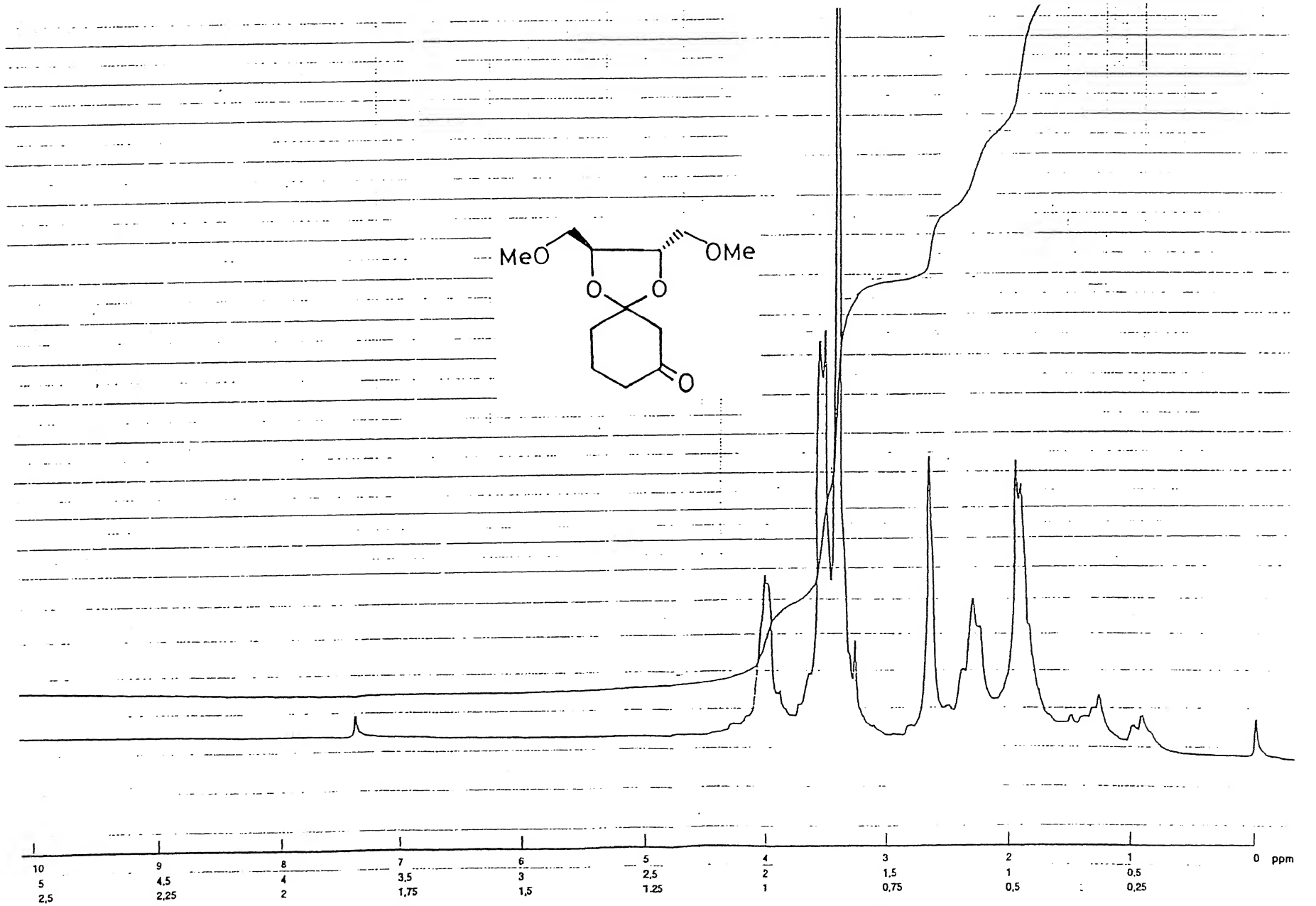
δ (ppm)

TMS

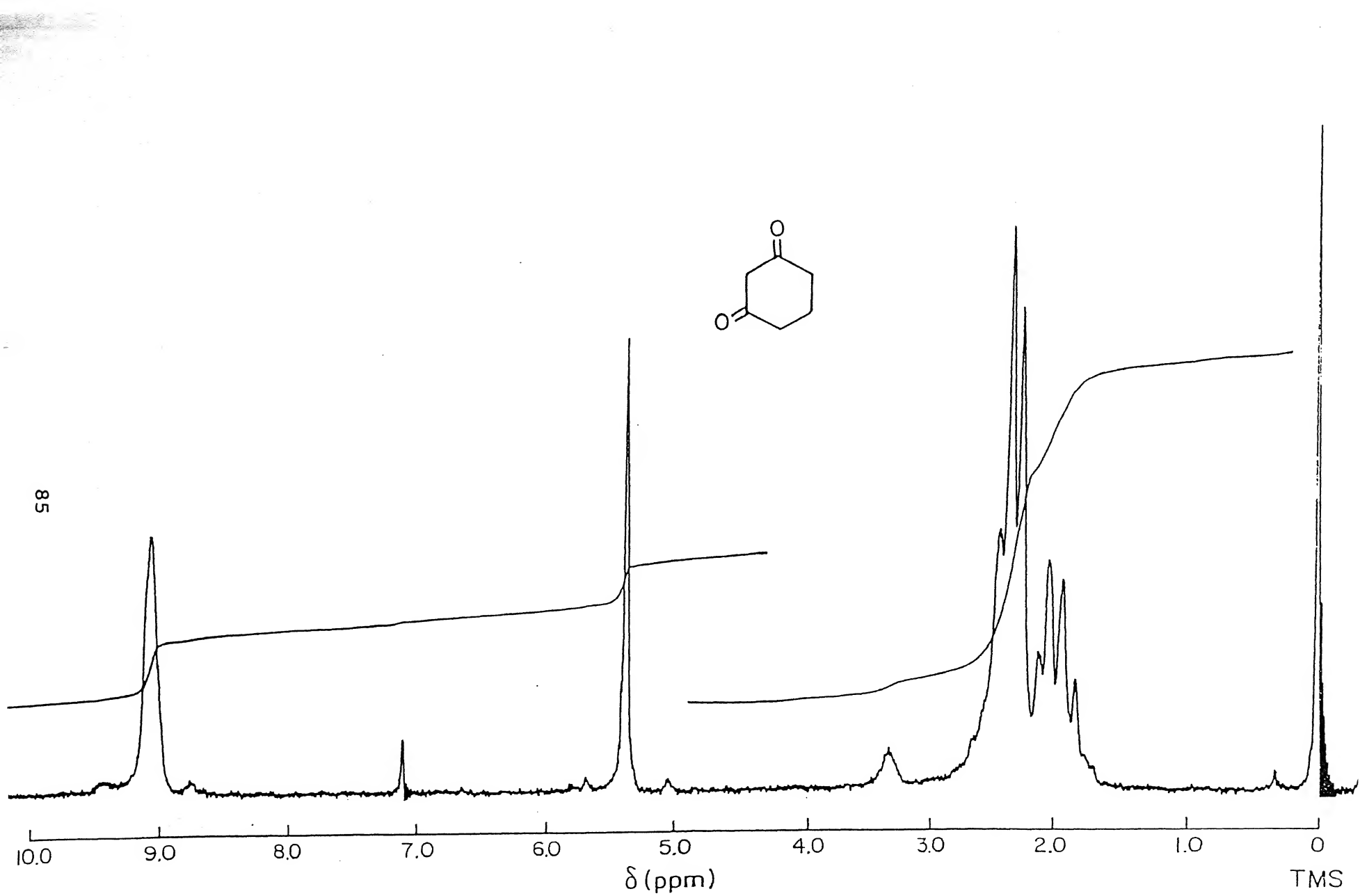
60 MHz ^{1}H NMR spectrum of the compound 93



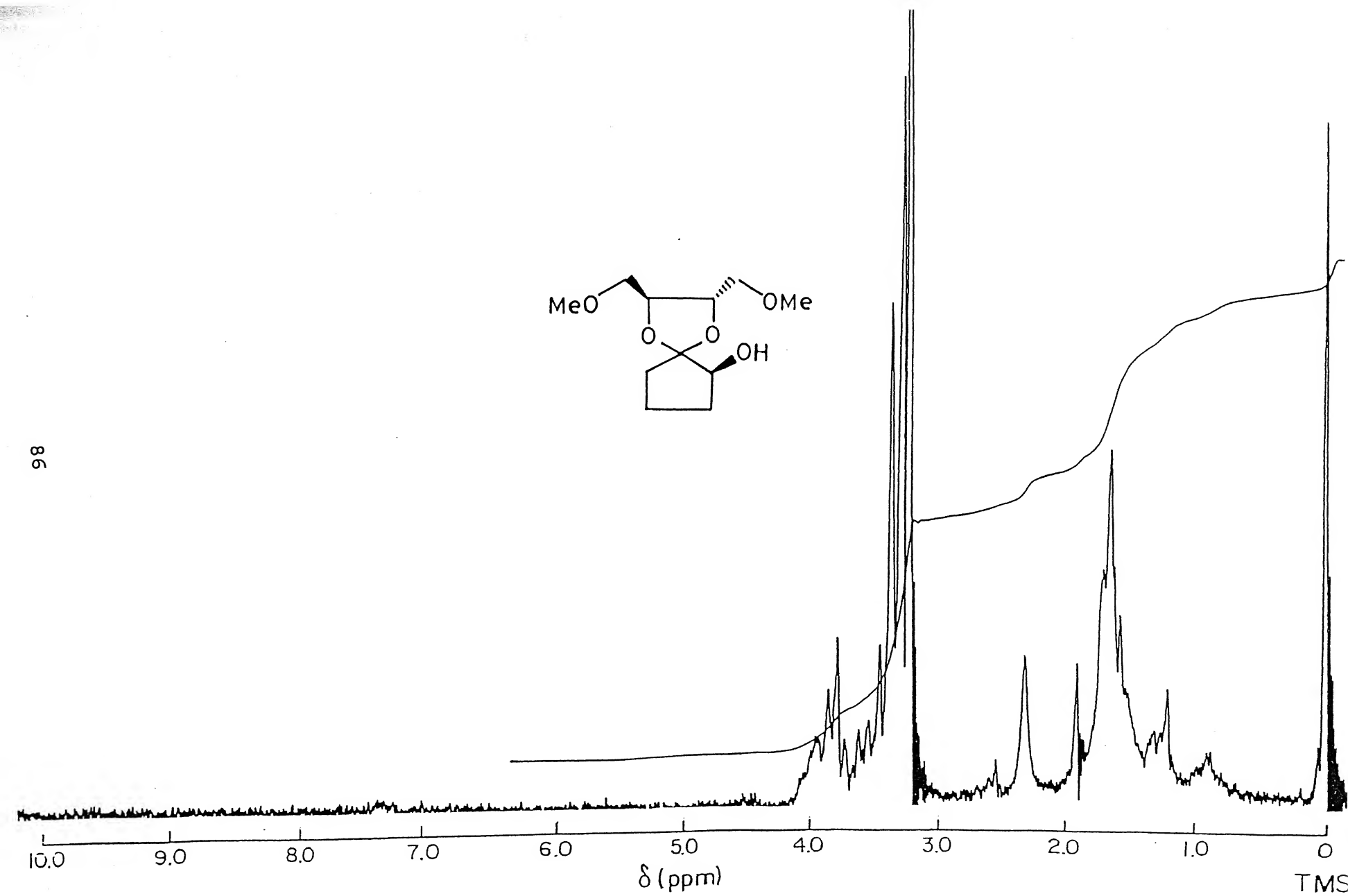
60 MHz ^{1}H NMR spectrum of the compound 91



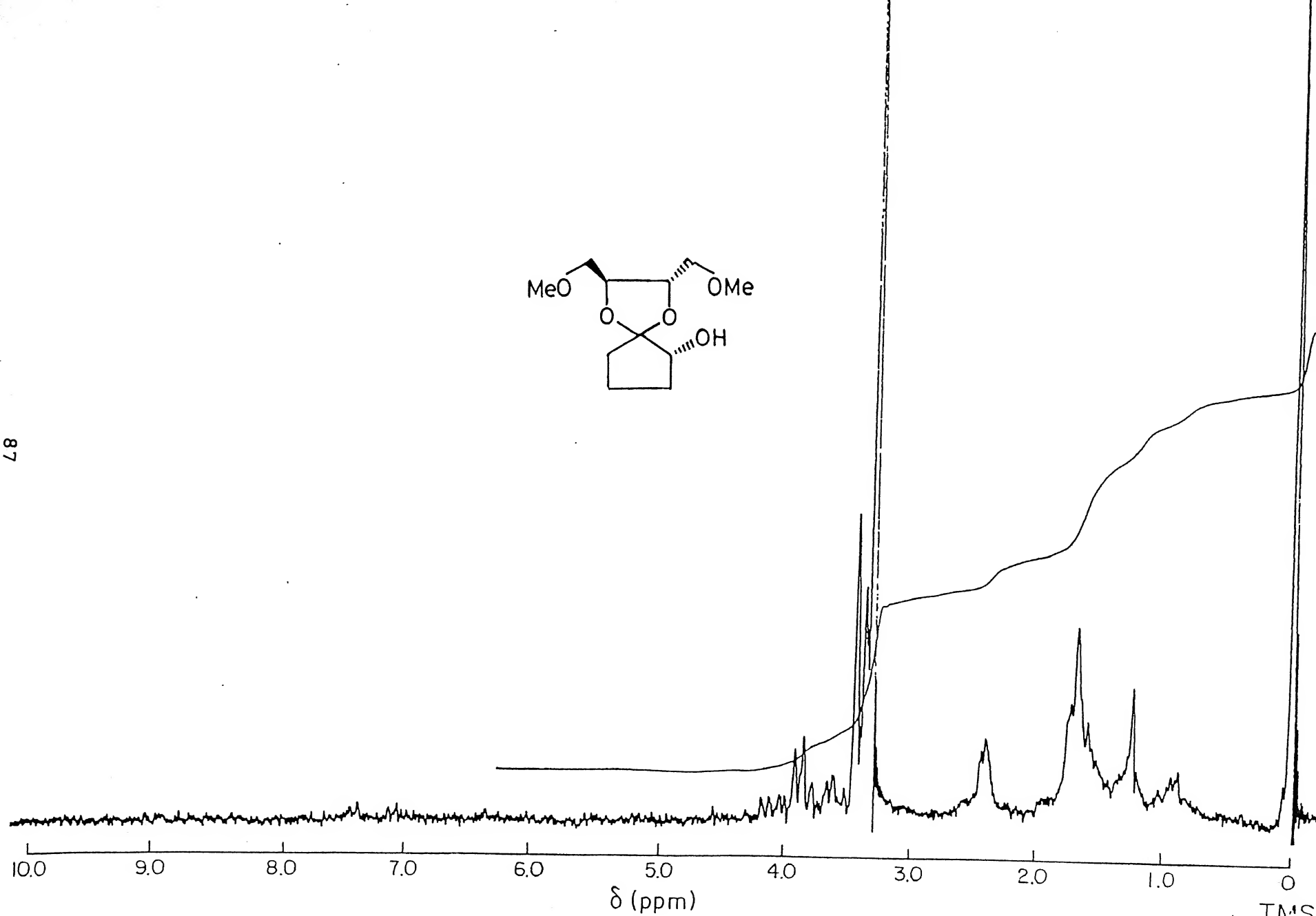
80 MHz ^{1}H NMR spectrum of the compound 106



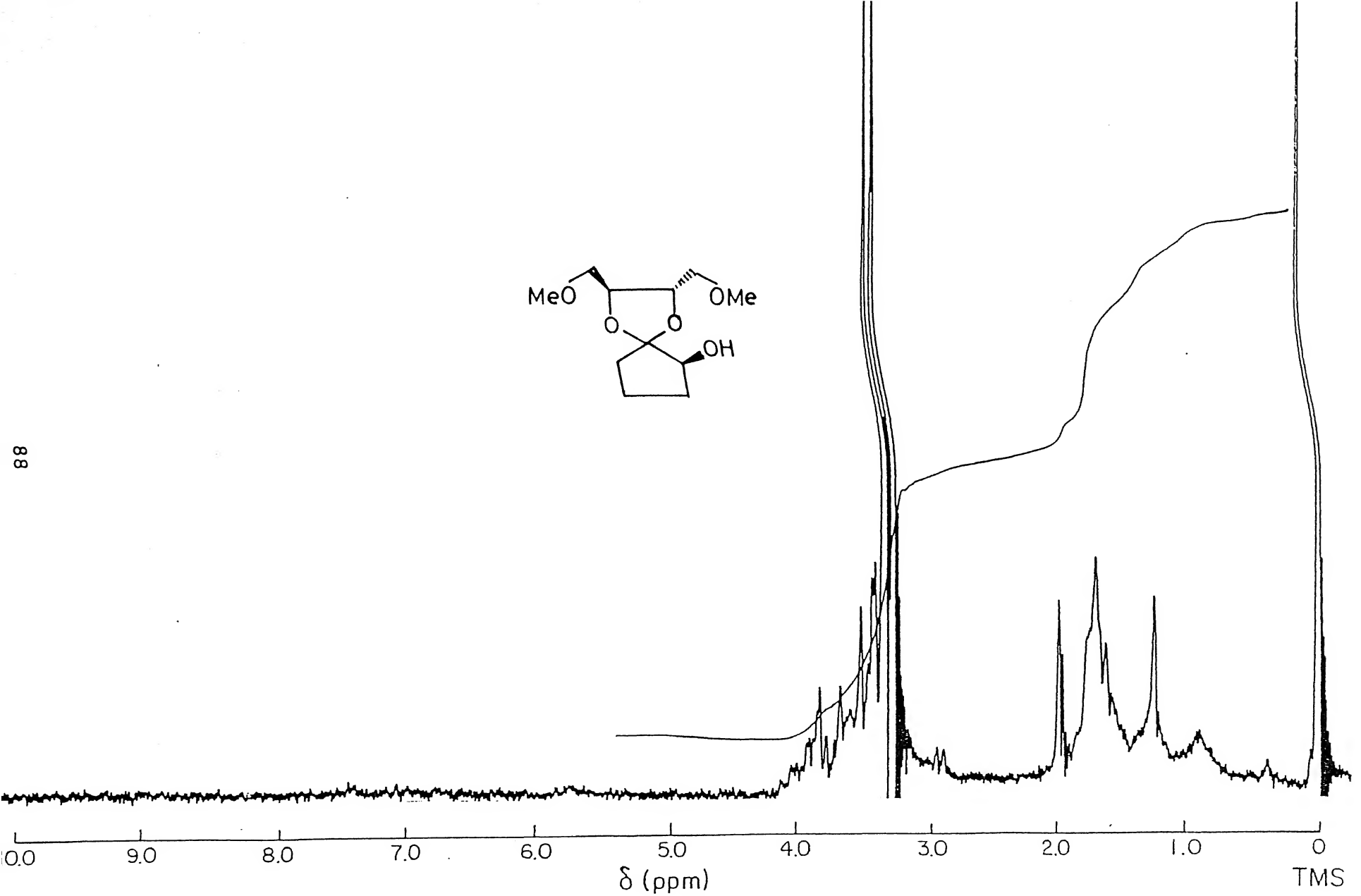
60 MHz ^{1}H NMR spectrum of the compound 95



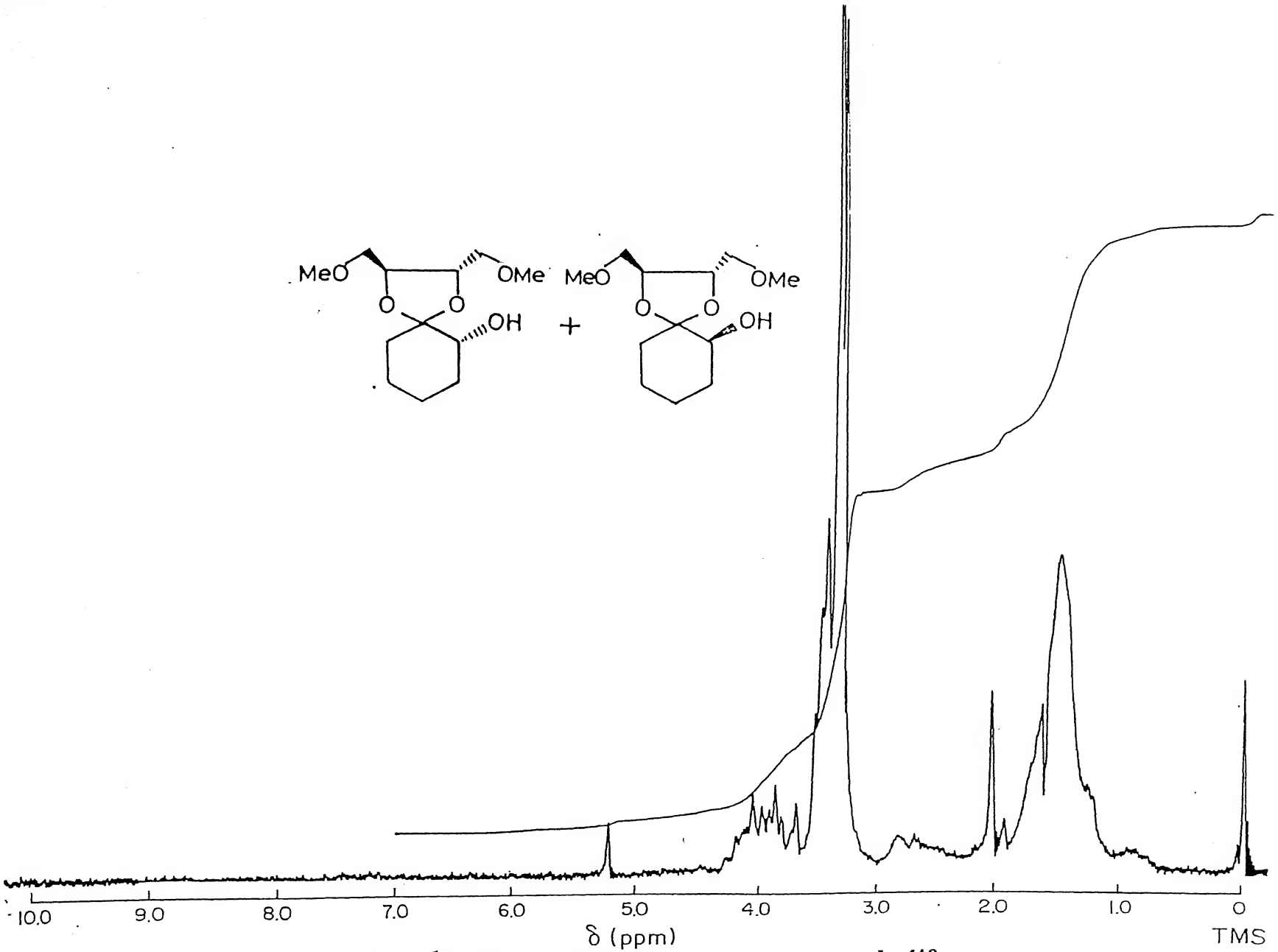
60 MHz ^{1}H NMR spectrum of the compound 108 A



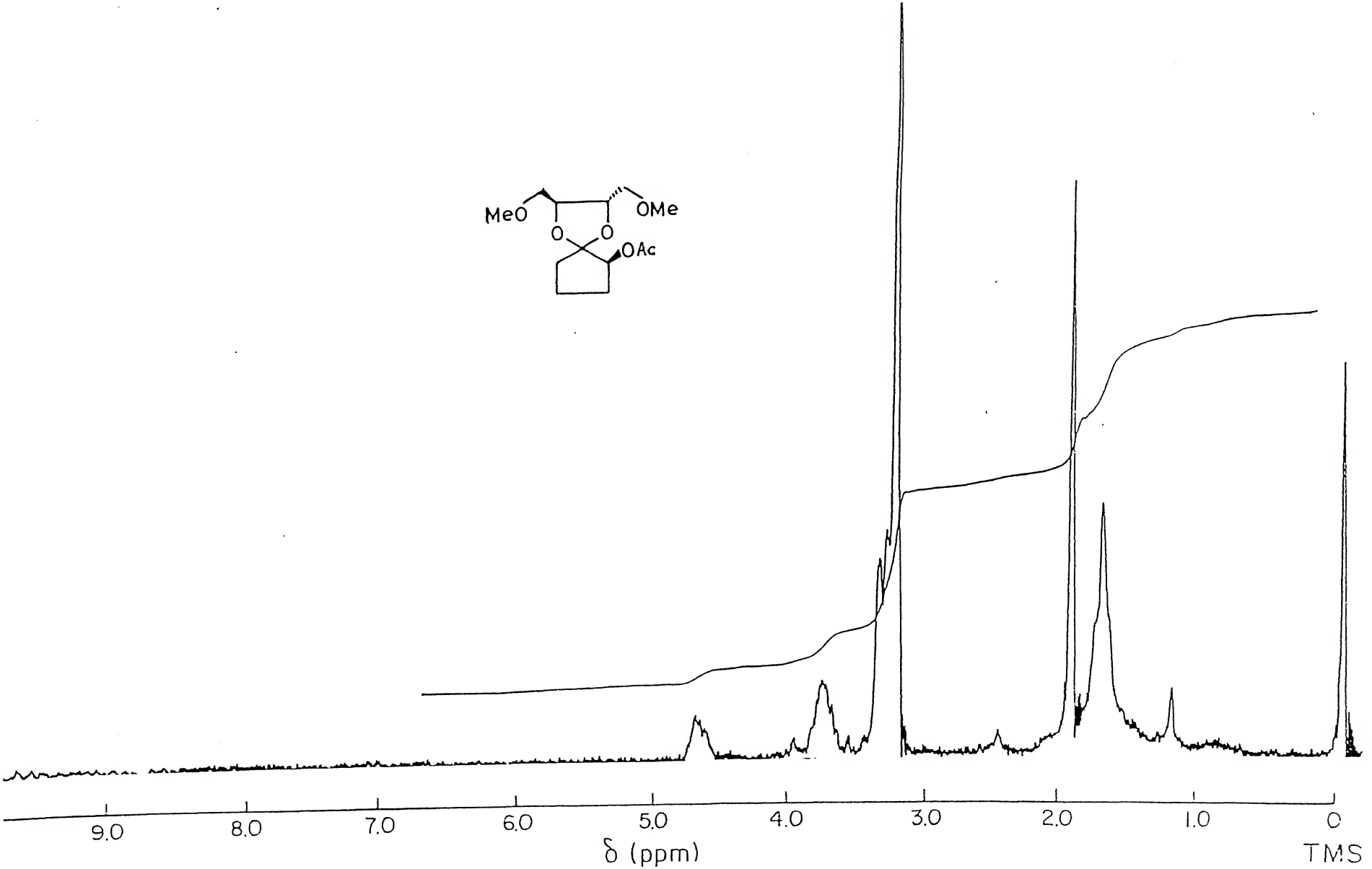
60 MHz ^{1}H NMR spectrum of the compound **108 B**



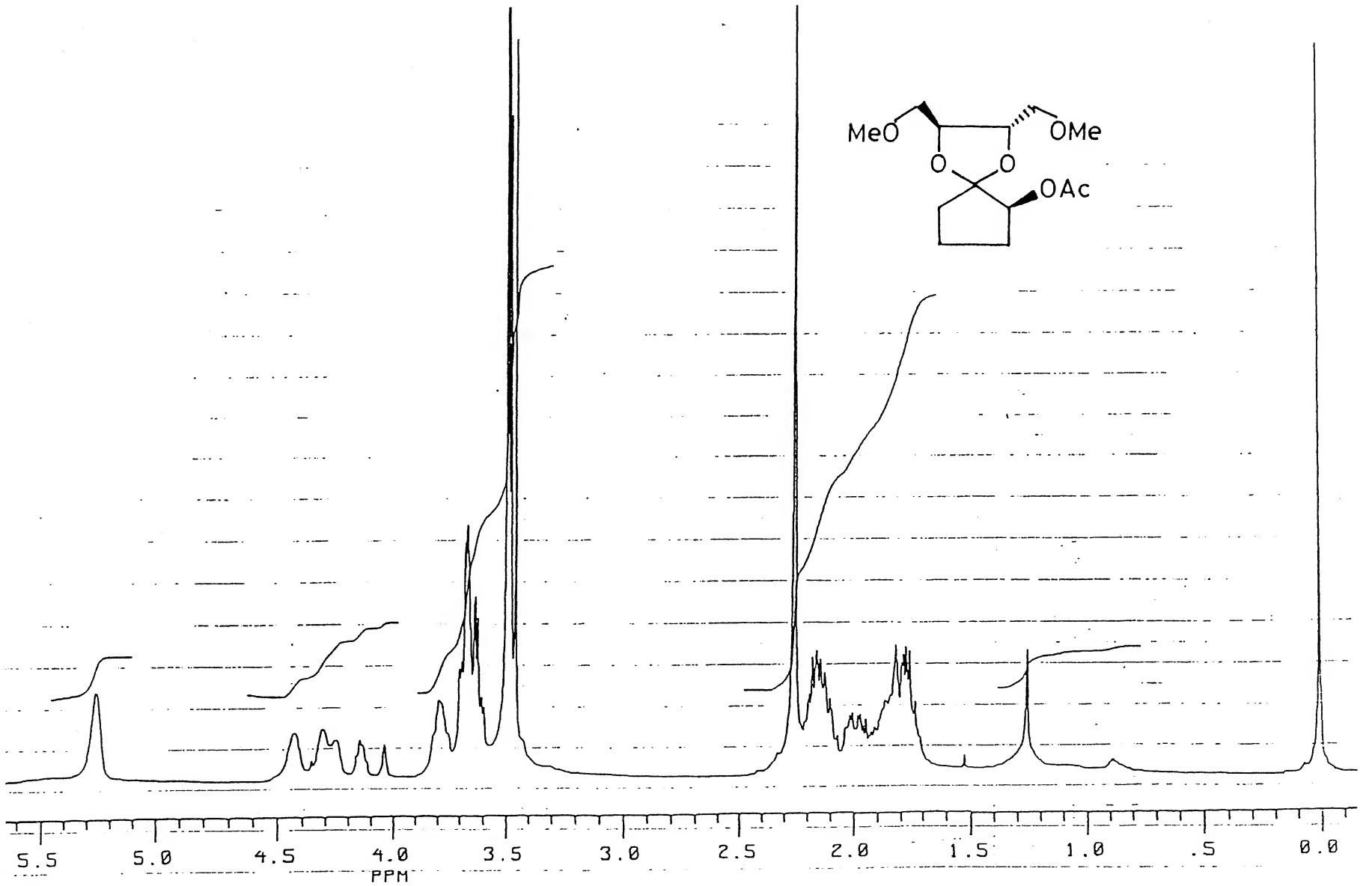
60 MHz ^{1}H NMR spectrum of the compound 108 c



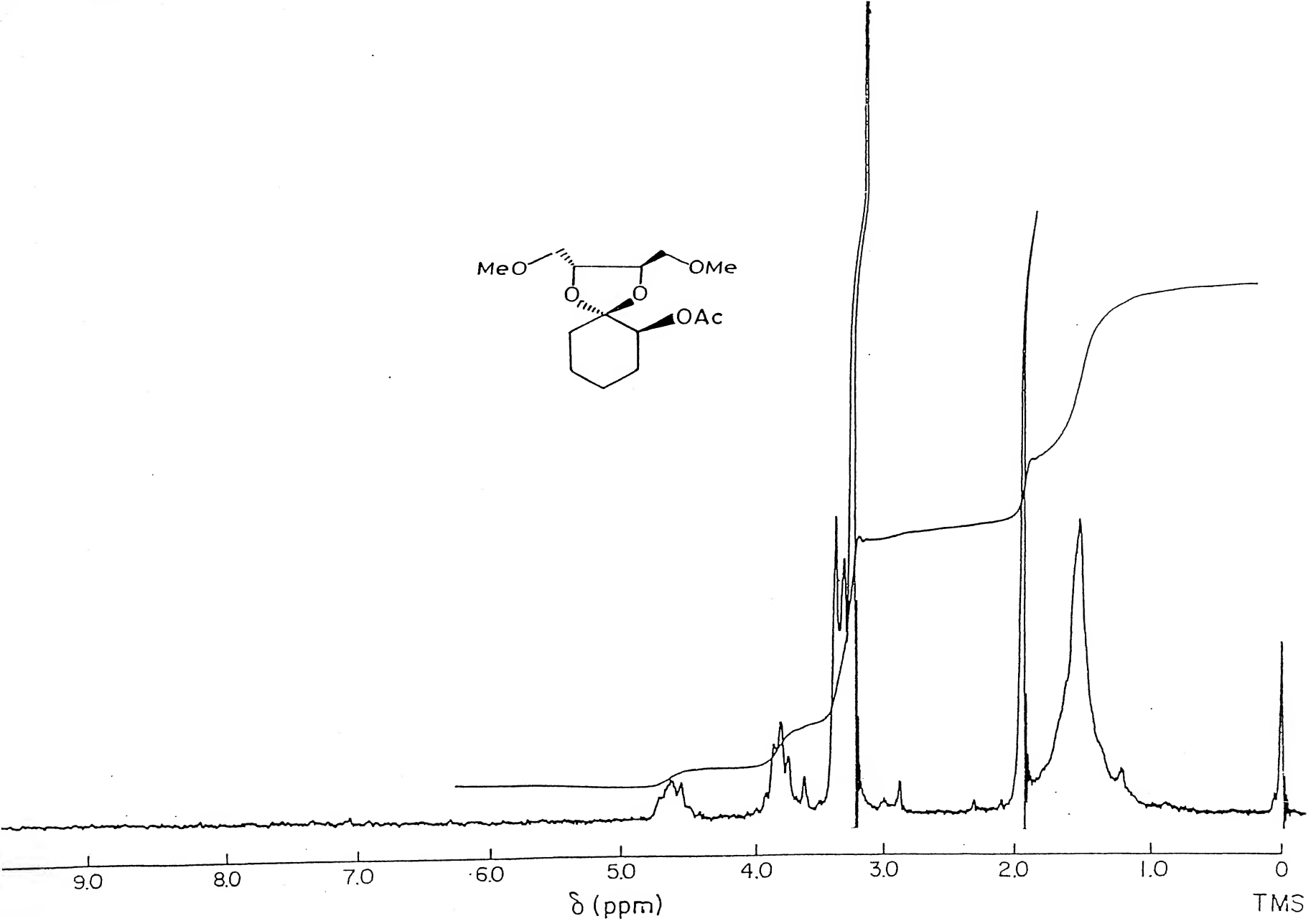
60 MHz ^{1}H NMR spectrum of the compound **112**



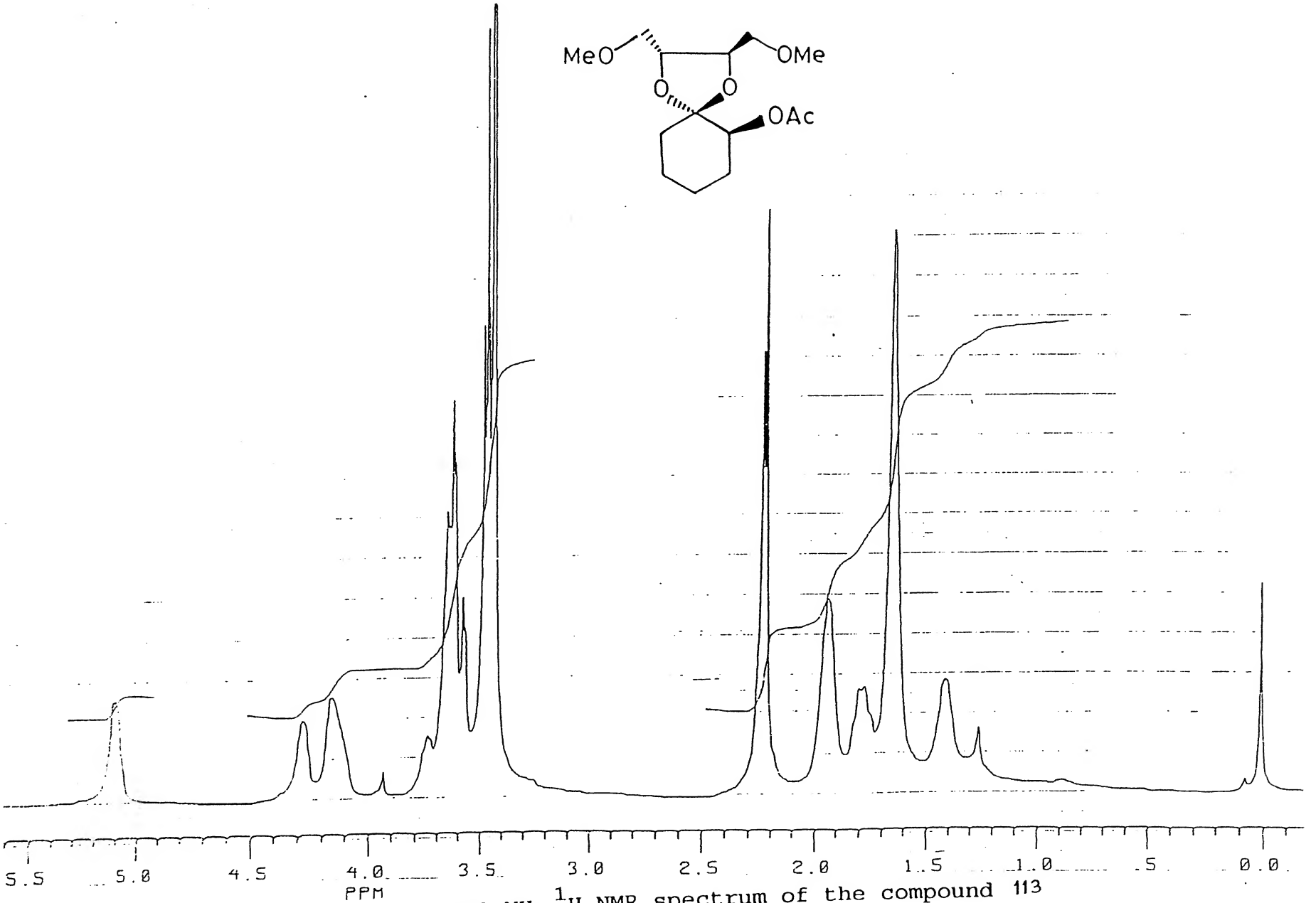
60 MHz ^{1}H NMR spectrum of the compound 109



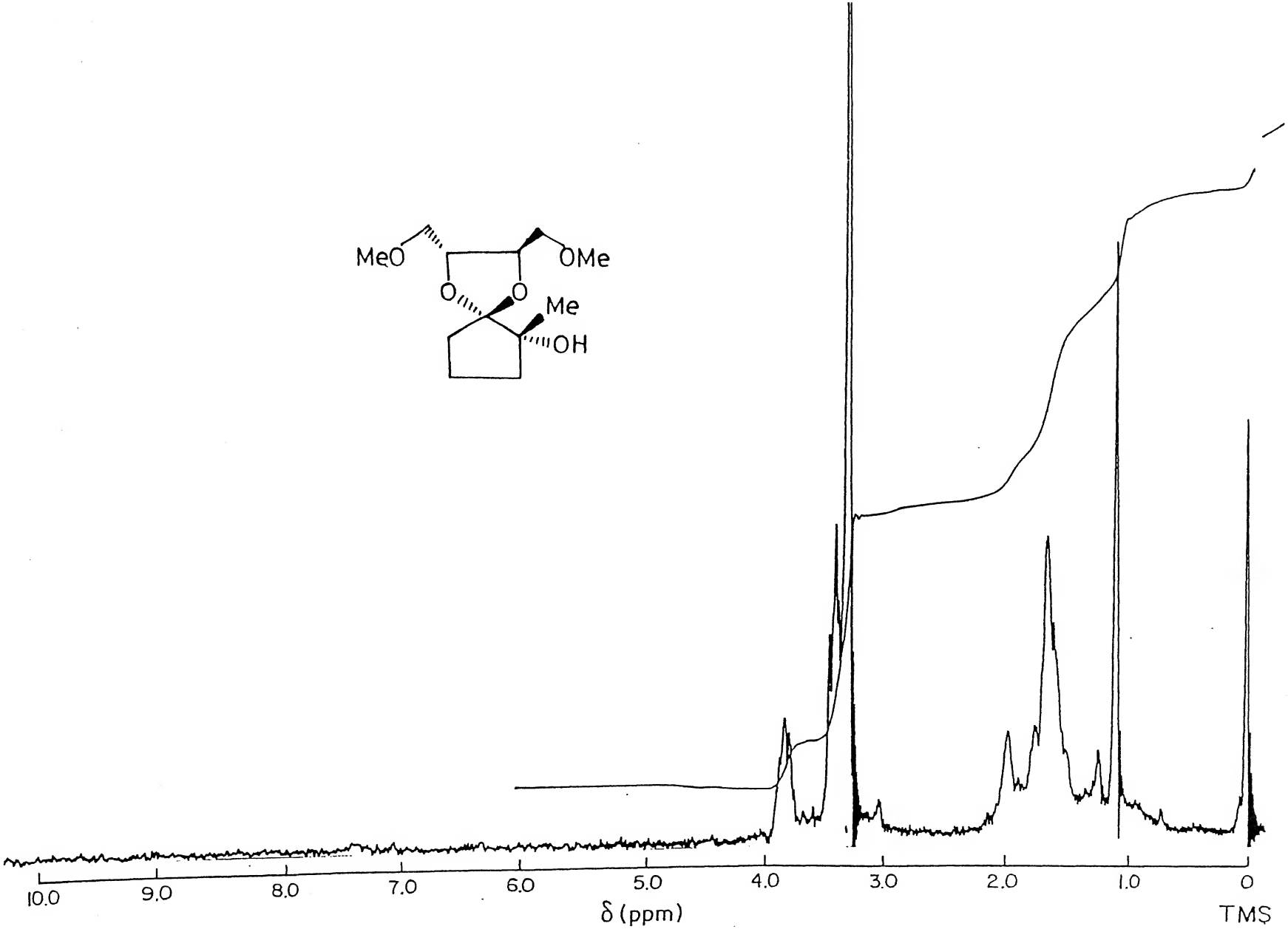
400 MHz ^{1}H NMR spectrum of the compound 109



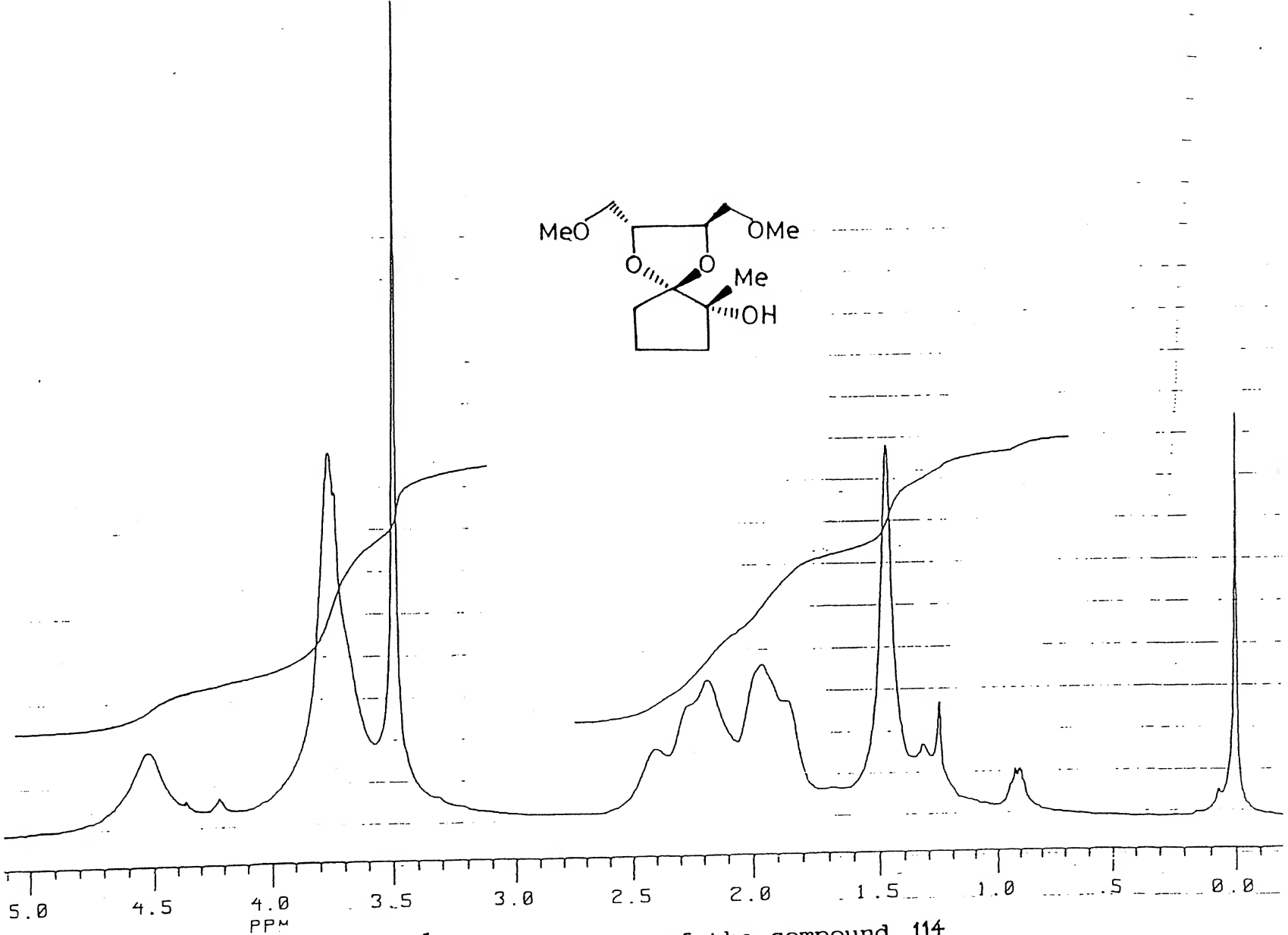
60 MHz ^{1}H NMR spectrum of the compound 113



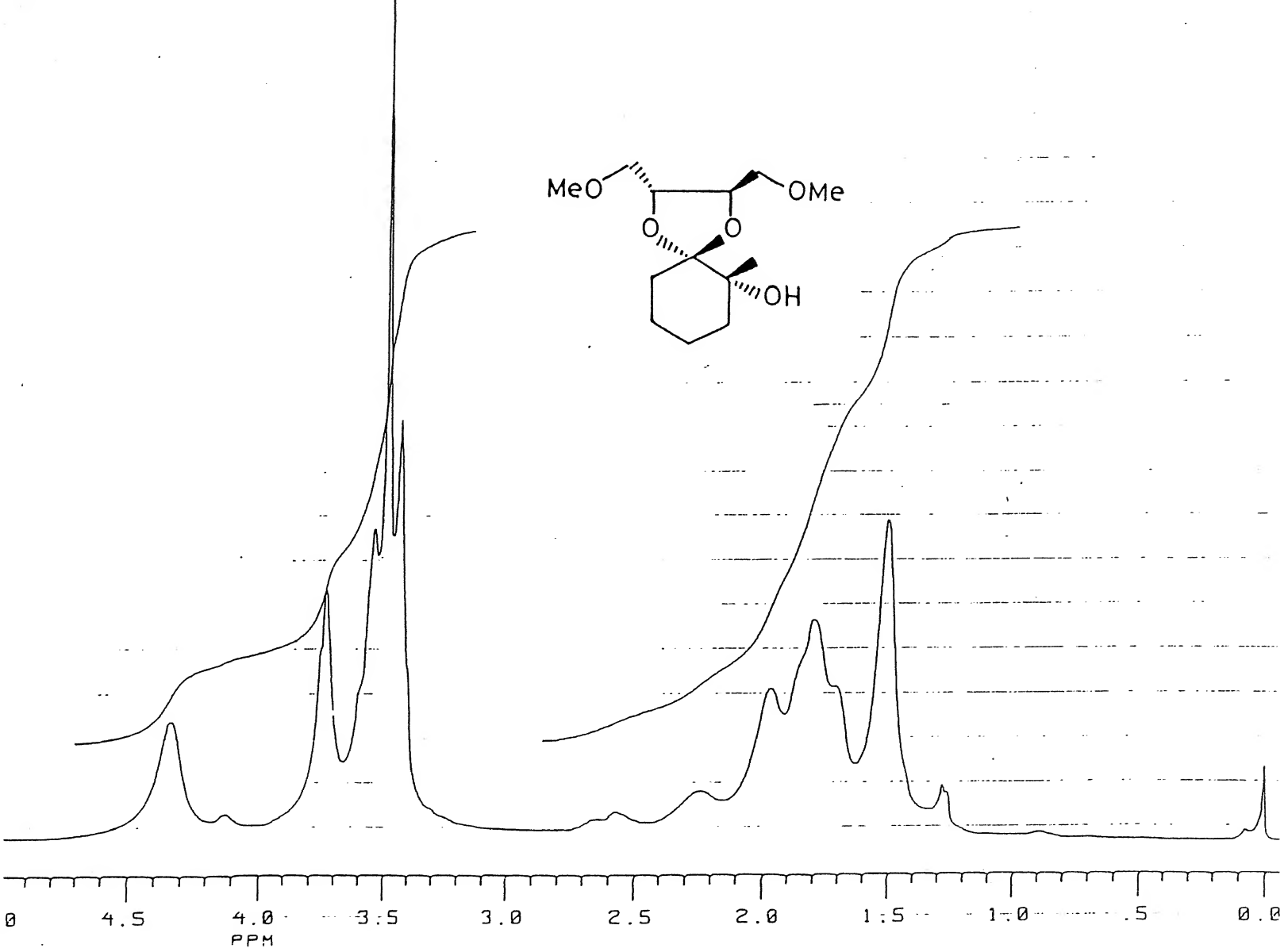
400 MHz ^{1}H NMR spectrum of the compound 113



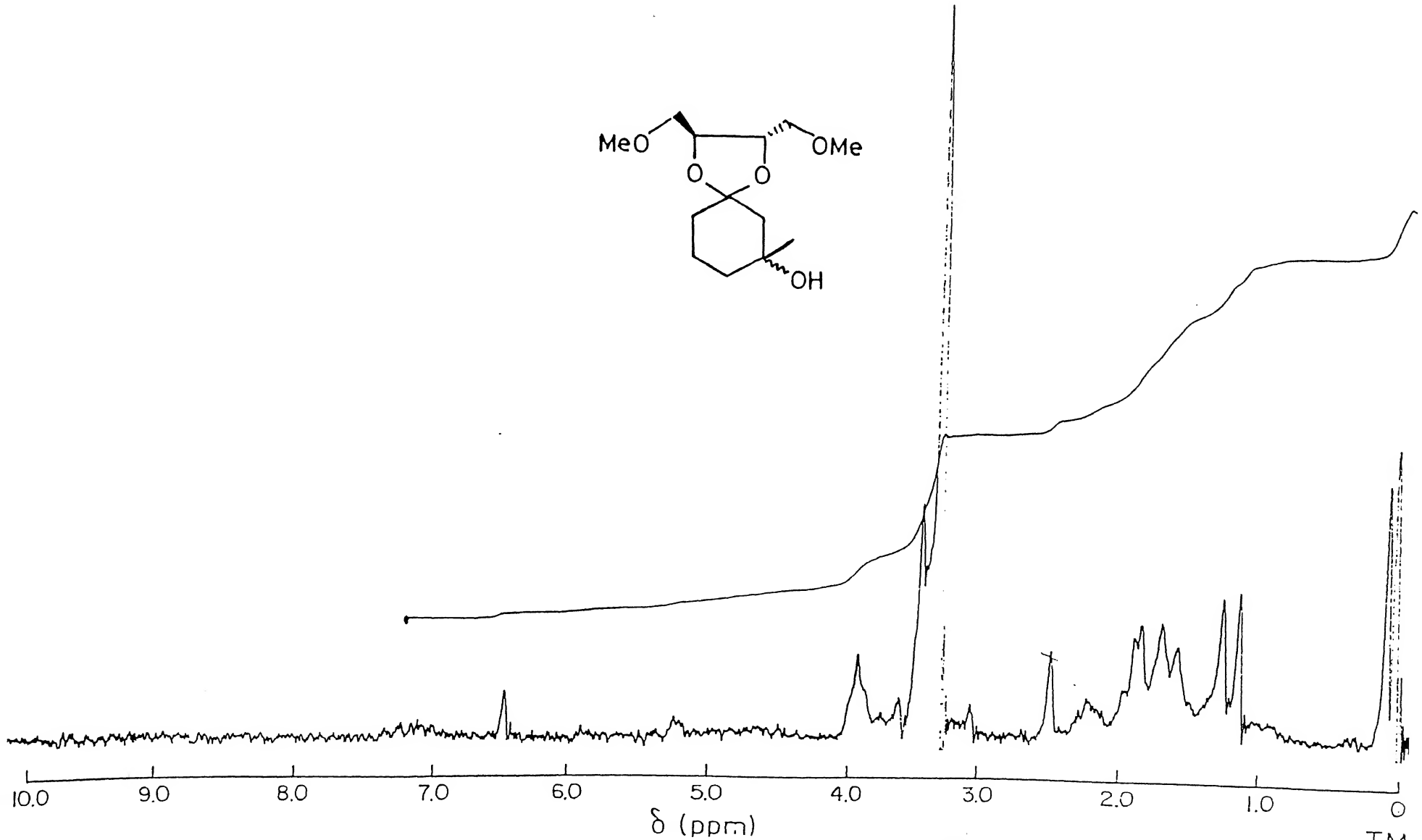
60 MHz ^{1}H NMR spectrum of the compound 114



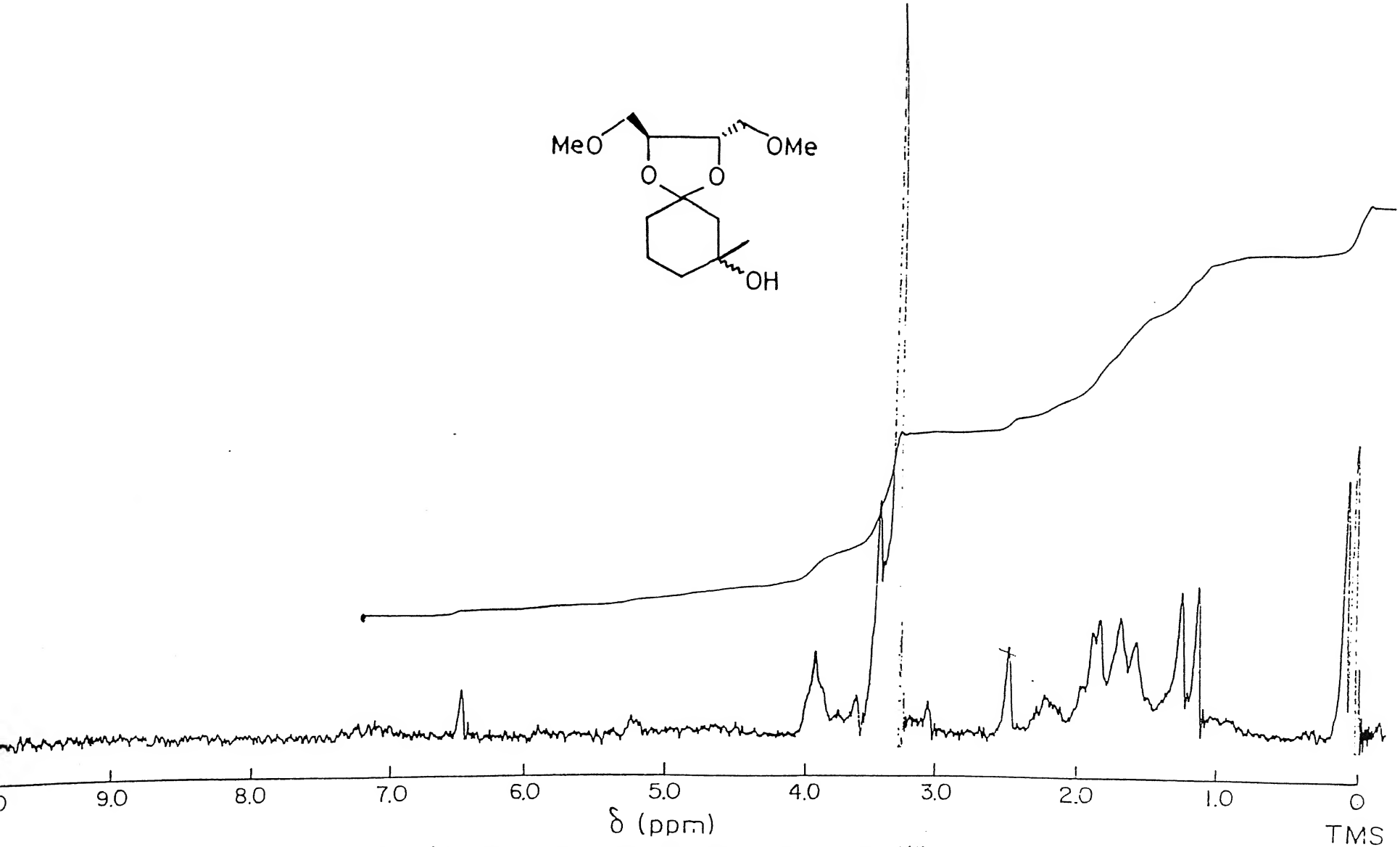
400 MHz ^{1}H NMR spectrum of the compound 114



400 MHz ^{1}H NMR spectrum of the compound 116



60 MHz ^{1}H NMR spectrum of the compound 115



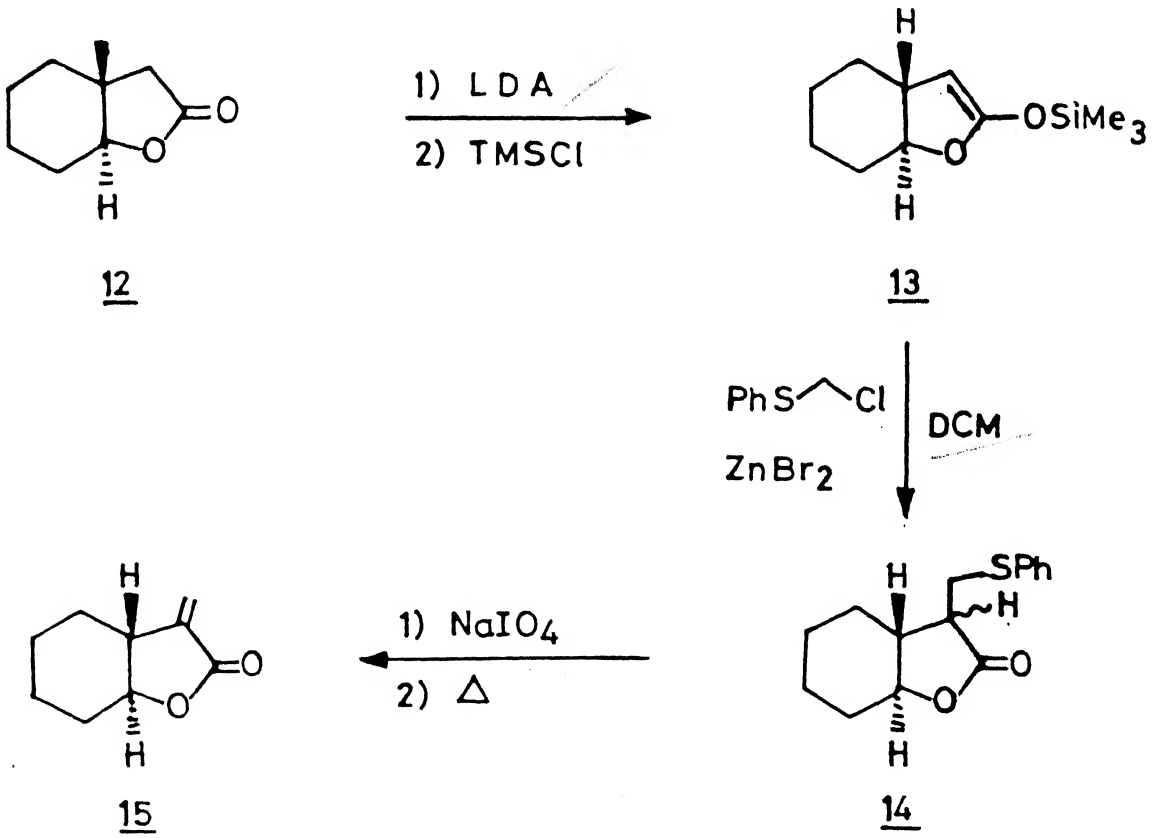
60 MHz ^{1}H NMR spectrum of the compound 115

CHAPTER I

PART B

EFFECT OF CHIRAL ACETALS ON RADICAL REACTIONS AND SYNTHESIS OF α-METHYLENE-γ-BUTYROLACTONES

Because of the importance of these compounds several routes their preparation have been developed as is evident from the erature[2,3]. A few approaches extrated from the literature are tioned in following few pages. Lactone or ester enolates, when st silylated, can be phenyl thiomethylated in high yields using oromethyl phenyl sulphide ($PhSCH_2Cl$) and mild Lewis acid alysis with zinc bromide. This provides an efficient method the α-methylenation of both lactones and ester[4] (Scheme 1).

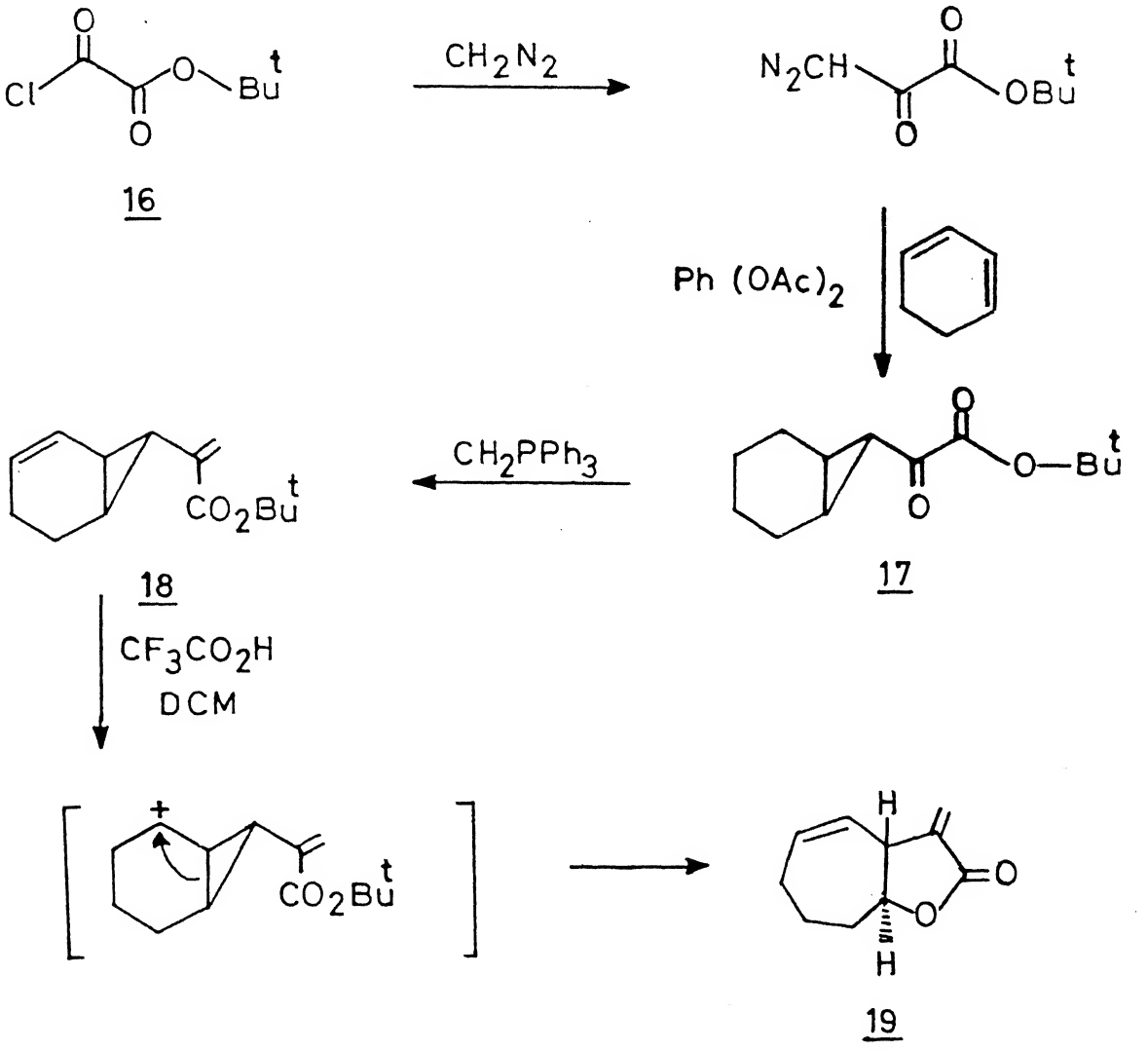


12 13 14 15

SCHEME - 1

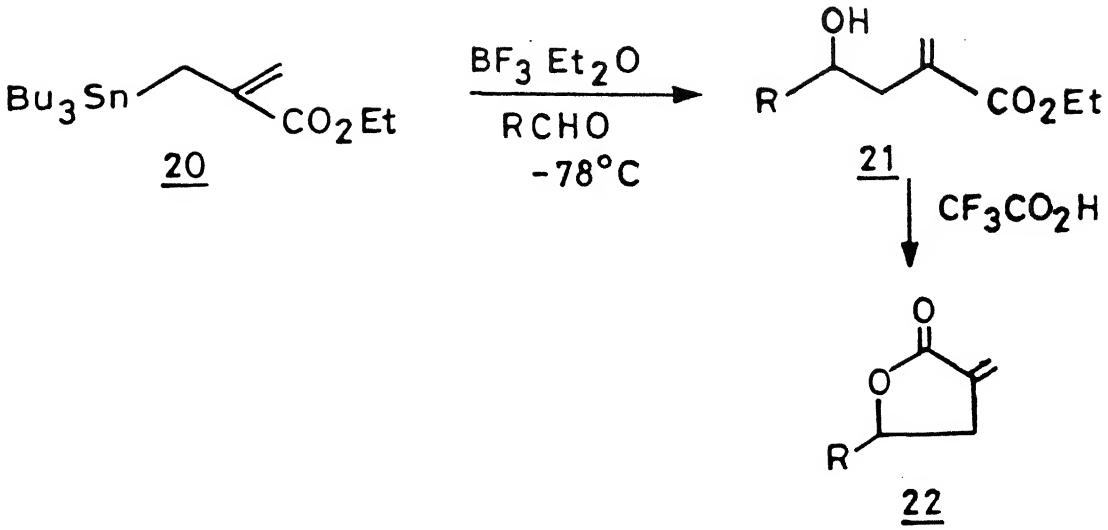
A stereospecific ring expansion synthesis of transfused -methylene-γ-butyro lactones can be accomplished in excellent

ld through the sequence of carbene addition of tert. butyl zopyruvate to cyclic dienes. Inverse Wittig condensation to e a tert-butyl ester substituted trans-divinyl cyclopropane and d catalyzed cleavage of the cyclopropane ring.[5] (Scheme 2).



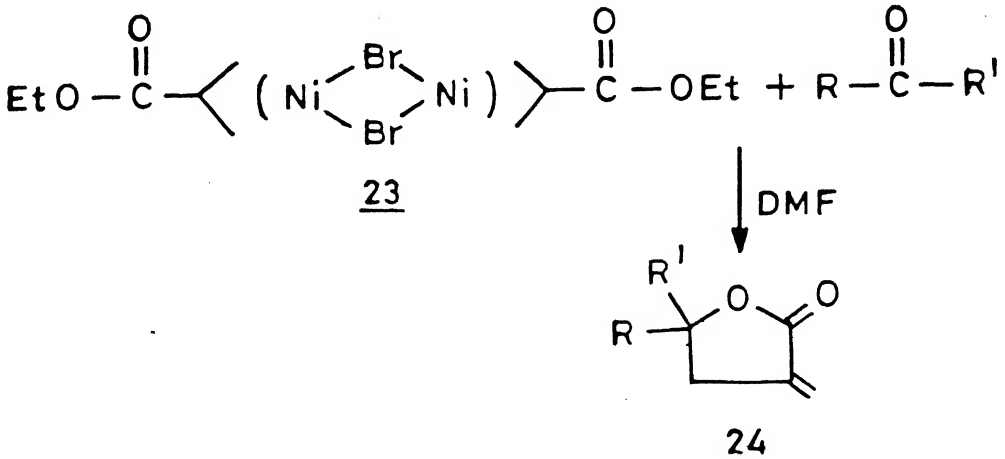
SCHEME - 2

When 2-ethoxy carbonyl allyl stannane is treated with an ldehyde in the presence of $BF_3.Et_2O$ followed by acid treatment, -methylene-γ-butyro lactones are formed[6] (Scheme 3).



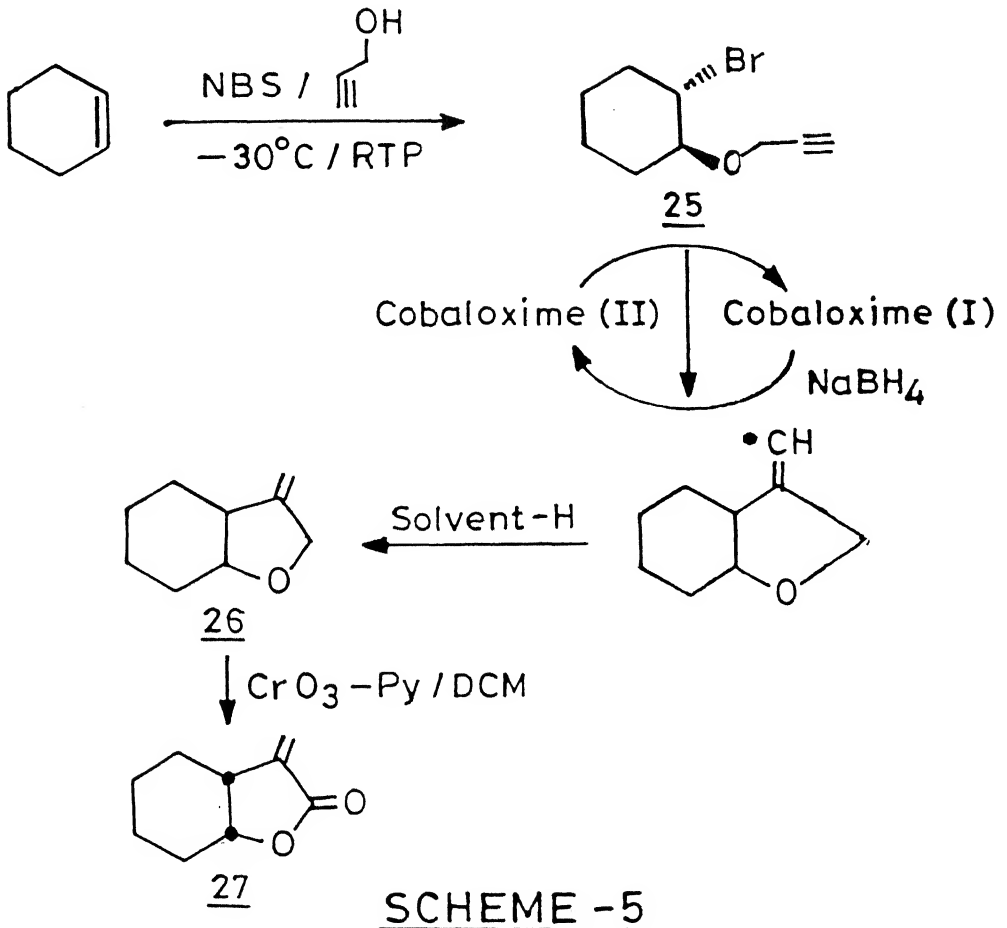
SCHEME -3

α-Methylene-γ-butyro lactones can also be obtained by eaction of π-allyl nickel bromide complexes with ketones and ldehydes. The reaction of π-2-(carbethoxy allyl) nickel bromide ith aldehydes and ketones leads to α-methylene-γ-butyro lactones[7] Scheme 4).



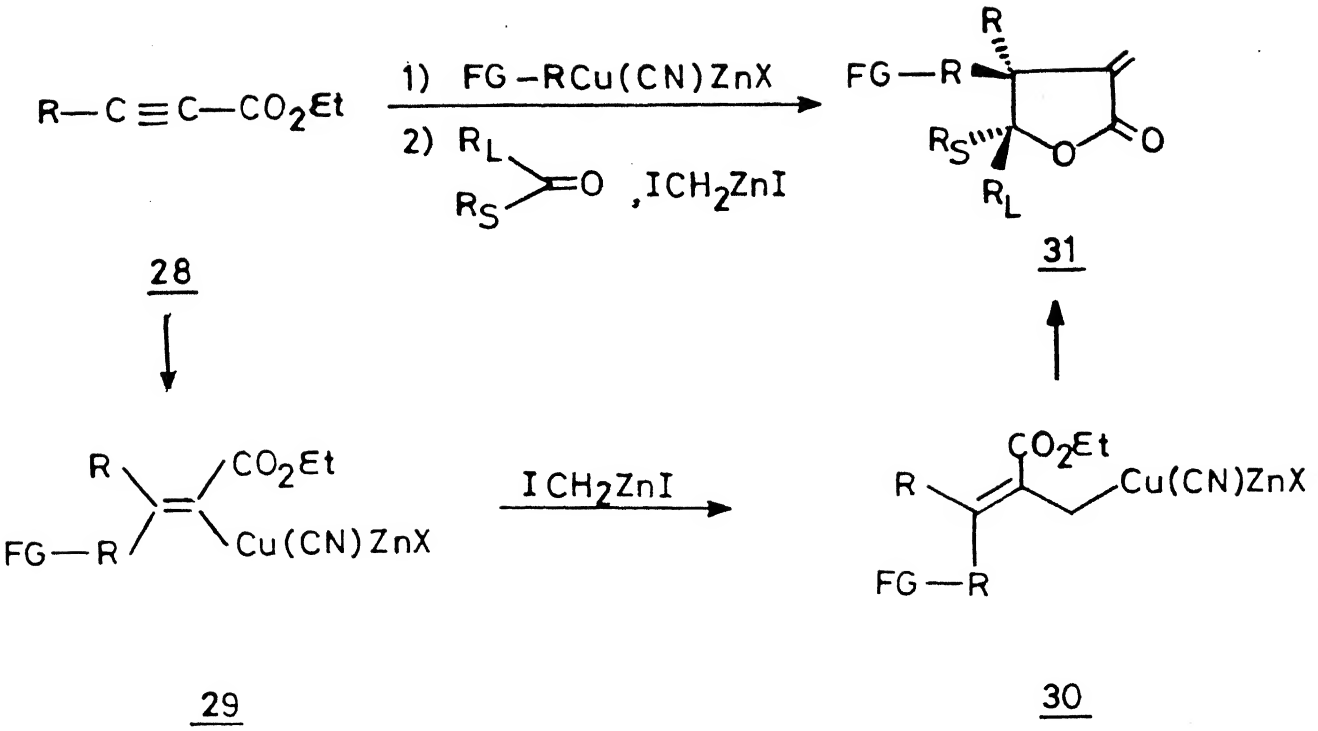
SCHEME -4

Radical cyclisation approach has been introduced to prepare α-methylene-γ-butyro lactones[8] in which the junction is always cis. (Scheme 5).



SCHEME -5

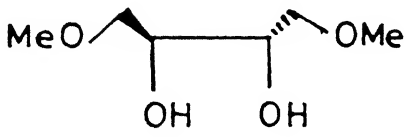
A new stereoselective one pot synthesis of highly functionalised α-methylene-γ-butyro lactones has been reported by Knochel et al[9]. It utilises an acetylenic ester, a readily prepared Zn-Cu reagent, an aldehyde or ketone and (iodo methyl) zinc iodide. (Scheme 6). Cis-trans ratio 100:0 to 75:25 have been reported for different substrates.


R—C≡C—CO2Et
1) FG-RCu(CN)ZnX
2) RL RS=O , ICH2ZnI
FG—R
R
RS
RL
O
O
28
31
R
CO2Et
FG—R
Cu(CN)ZnX
ICH2ZnI
CO2Et
R
Cu(CN)ZnX
FG—R
29
30

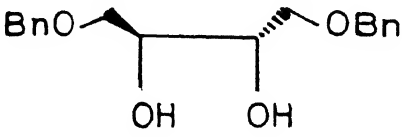
SCHEME-6

I.B.2 RESULTS AND DISCUSSION

From the introduction part of this chapter it is clear that because of the associated biological activity with α-methylene-γ-butyro lactones a number of approaches towards their synthesis have been developed. Excellent reviews have been published in the recent past in this regard. Despite this progress, it appears important to develop many more approaches towards their synthesis and especially for the optically active units with appropriate functionalisations for further elaboration. With this view in mind and also because of our ongoing project on chiral acetals, we decided to study the effect of chiral acetals on radical cyclisation reactions in synthesizing α-methylene-γ-butyro lactones. We have chosen the following two diols for preparing chiral acetals from appropriate carbonyl compounds.



A



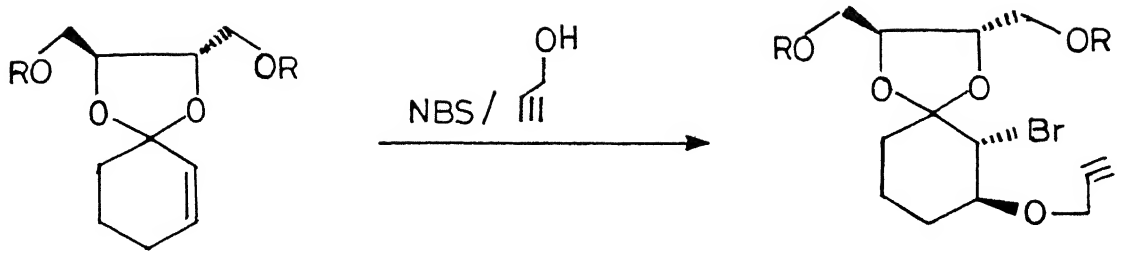
B

The diol A is the same diol which is utilised in part 'A' of this chapter. The diol B was prepared by benzylation of 120 (cf. part 'A') with benzyl bromide. The two diols were chosen as to find out the effect of the methoxy methyl and the benzyloxy methyl group on the diastereoselection during radical cyclisation. The

procedure for the synthesis of α-methylene-γ-butyro lactones was similar to the one shown in the scheme 5 of the introduction part except that in place of a cobaloxime, we employed n-Bu_3SnH/AIBN combination for the intramolecular cyclisation using radical chemistry.

To find out the effect of chiral acetals on radical cyclisations, we chose two cyclic (i.e., 31 and 32) and two acyclic (i.e., 43 and 44) olefinic acetals (cf. Scheme 7). Compound 31 is the same as that employed in Part A of this chapter (cf. compound 99). Compound 32 was also synthesized in a manner analogous to the one for 99. Separate reactions of 31 and 32 with n-bromosuccinimide in the presence of propargyl alcohol gave the corresponding addition products 33 and 34 in 96% and 70% yield respectively. As in the case of bromohydrin in Part A of this chapter addition of the elements of Br and propargyl alcohol appeared to be highly regiospecific with Br being added at 'α' position to the acetal and propargyl alcohol 'β' to the acetal.

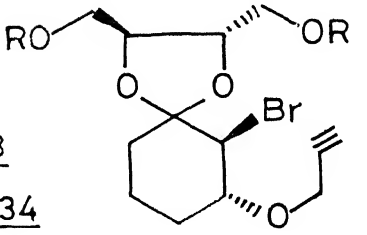
Compound 33 showed in its IR spectrum absorptions at 3280 (-C≡C-H), 2105 (-C≡C-) cm^{-1}. Its ^1H NMR spectrum displayed signals at δ 4.47 (2H, t, $-OCH_2-C\equiv CH$, J = 2 Hz), 4.43-3.8 (4H, m, H-C(-O-)-, -CHBr and methines), 3.67-3.3 (10H, m, containing a 6H, s, at 3.4, $2X-CH_2OCH_3$), 2.43 (1H, t, -C≡CH, J = 2 Hz) and 2.03-1.3 (6H, m, $3X-CH_2-$). The mass spectrum indicated a weak molecular ion peak at 364 corresponding to its molecular weight. Likewise, compound 34 showed IR absorptions at 3280 and 2110 cm^{-1} and ^1H NMR spectrum indicated peaks at δ 1.3-1.9 (6H, m, aliphatic), 2.45 (1H, t, -C≡C-H, J = 2 Hz), 3.65-3.7 (4H, d, $2X-CH_2O-$), 3.9-4.4



R = −Me 31

R = $-CH_2Ph$ 32

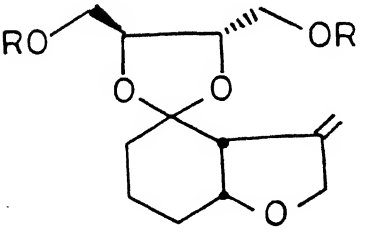
+



R = −Me 33

R = $-CH_2Ph$ 34

TBTH/AIBN

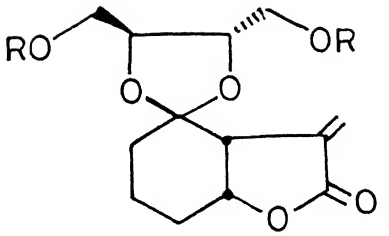


R = $-CH_3$ 35

R = $-CH_2Ph$ 36

CrO_3 / Py

DCM



R = $-CH_3$ 37

R = $-CH_2Ph$ 38

SCHEME -7

(6H, m, -CHBr, -HC-O-, $-OCH_2-C\equiv C-$, methines), 4.45-4.70 (4H, d, $PhC\underline{H}_2OX2$), 7.2-7.52 (10H, m, aromatic).

Compound 33 and 34 were subjected to radical cyclisation at 80°C with tributyltin hydride and catalytic amount of AIBN in benzene. The reaction took place smoothly to give the bicyclic ethers 35 and 36 in 60% and 65% yield respectively. Analysis of ^1H NMR spectrum of compound 35 revealed that the two olefinic protons are at δ 5.23-5.0 and δ 4.9-4.7 as two multiplets. The other signals were as follows : a 5H, m, at δ 4.27-3.75 ($-C\underline{H}OC\underline{H}_2C=$ and 2H, methines), a 10H, m, at δ 3.6-3.3 ($2X-CH_2OCH_3$), a 1H, m at δ 2.8-2.5 ($-\underset{|}{C}H-\underset{|}{C}=$) and a 6H, m at δ 2.0-1.35 ($3X-CH_2$, aliphatic). Similarly compound 34 has ^1H NMR signals 1.17-1.85 (6H, m, aliphatic), 2.5-2.8 (1H, m, $-\underset{|}{C}H-\underset{|}{C}=$), 3.4-3.68 (4H, m, $-CH_2O-X2$), 3.85-4.0 (3H, m, $-C\underline{H}_2O-C\underline{H}$), 4.08-4.25 (2H, m, methines), 4.35-4.52 (4H, s, $PhC\underline{H}_2O-X2$), 4.7-4.85 (1H, m, olefinic), 5.0-5.19 (1H, m, olefinic), 7.0-7.35 (10H, m, aromatic). Mass spectrum of this compound at 436 corresponded to its molecular weight.

These two compounds 35 and 36 upon oxidation with CrO_3-Pyridine complex in refluxing dichloromethane produced α-methylene-γ-butyro lactones 37 and 38 in 70% and 60% yields respectively (cf. Table 1). Compound 37 had its IR absorptions at 3010 ($=CH_2$), 1760 (-C=O, lactone) cm^{-1} and ^1H NMR analysis indicated δ 6.07 (1H, t, olefinic, J = 2 Hz), 5.87-5.67 (1H, m, olefinic), 4.7-4.33 (1H, m, $H-\underset{|}{C}-O-$), 4.07-3.73 (2H, m, methines), 3.6-3.3 (10H, m, containing a 6H, s at δ 3.33, $2X-CH_2OCH_3$), 3.07 (1H, dd, $-\underset{|}{C}\underline{H}-\underset{|}{C}=CH_2$, J = 2 Hz, 6 Hz) and 2.0-1.4 (6H, m, $3X-CH_2-$). Mass spectrum indicated molecular ion peak at 298. Similarly

compound 38 indicated IR absorption at 1760 cm^{-1} for lactone and ^1H NMR spectrum had peaks at δ 1.17-1.85 (6H, m, aliphatic), 2.9-3.1 (1H, m, -CH-C=), 3.52-3.70 (4H, d, $2XCH_2O$, J = 4 Hz), 3.85-4.10 (3H, m, HC-O-, methines), 4.34-4.6 (4H, s, $PhCH_2$-O-X2), 5.6-5.87 (1H, m, olefinic), 6.04-6.17 (1H, m, olefinic), 7.09-7.34 (10H, m, aromatic). High resolution ^1H NMR spectra (400 MHz) of lactones 37 and 38 using $Eu(hfc)_3$ as shift reagent indicated that the diastereoselectivity of these reactions was not high. Compound 37 showed 14% diastereoselectivity and 38 showed only 9%. The poor selectivity could be due to the fact that during the bromo propargylation step the two diastereomers were formed in equal ratio. Since the 'β' carbon is already having the mixture of isomers, the generation of radical 'α' to the acetal followed by cyclisation eventually gave almost racemic mixtures.

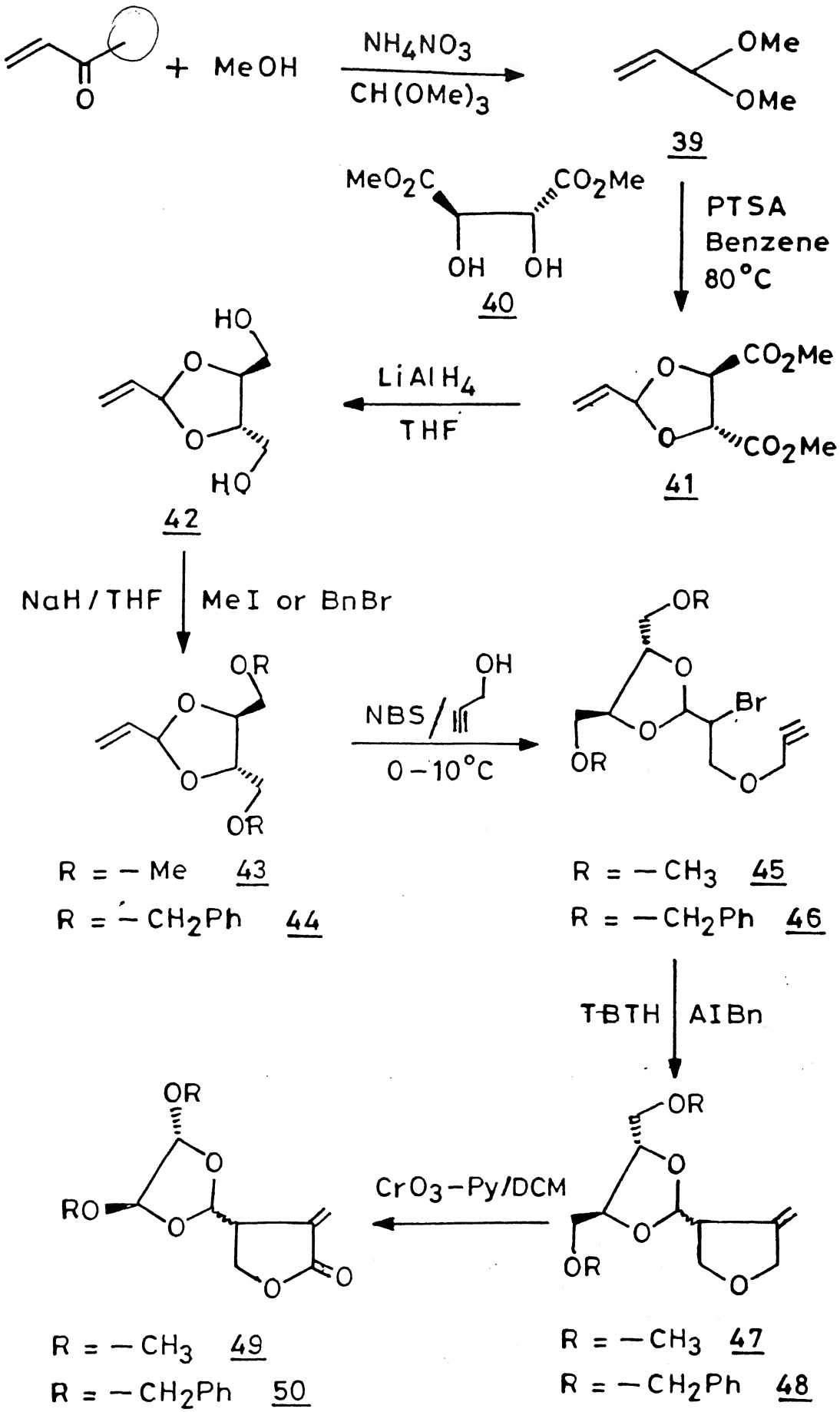
In order to circumvent this problem we studied the generation of one stereocentre. For this purpose we chose acrolein as a probe. The olefinic acetal 41 was prepared by a literature procedure[9]. Scheme - 8 Acrolein was treated with methanol and trimethylorthoformate in the presence of catalytic amount of ammonium nitrate to get acrolein dimethyl acetal 39. This was then exchanged with dimethyl tartarate 40 in the presence of catalytic amount of p-toulene sulfonic acid as acid catalyst to obtain olefinic acetal 41. The olefinic acetal 41 was reduced with $LiAlH_4$ to obtain the diol 42 which upon methylation gave dimethoxy olefinic acetal 43 and upon benzylation gave dibenzyloxy olefinic acetal 44. The structures of these compounds are in complete agreement with the spectral data. Olefins 43 and 44 were then treated with N-bromosuccinimide and propargyl alcohol at 0°C

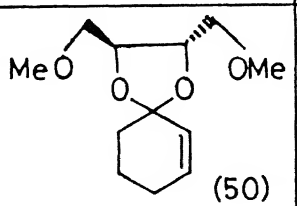
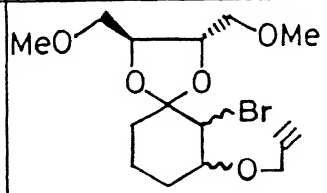
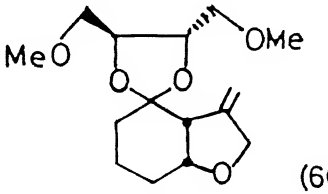
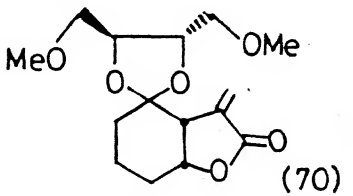
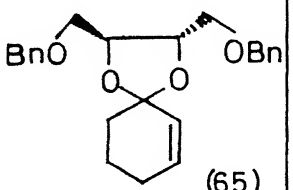
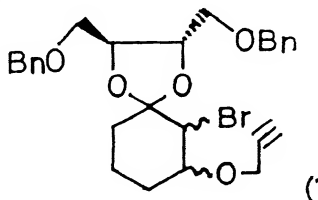
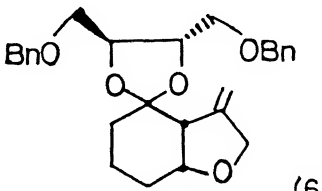
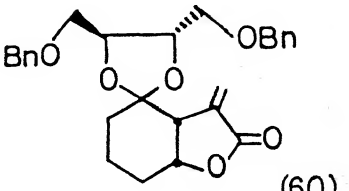
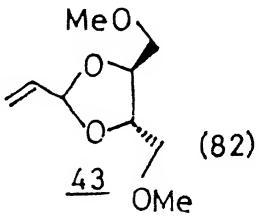
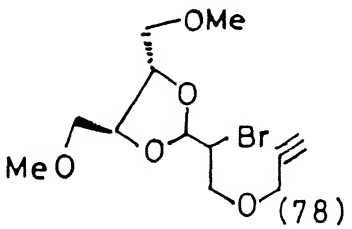
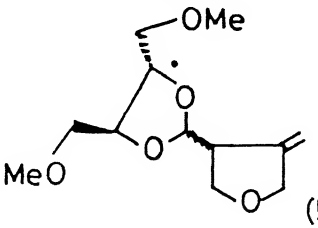
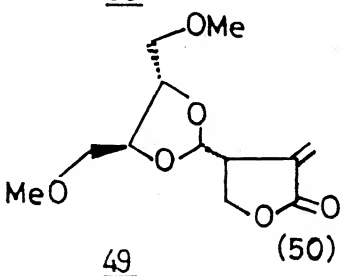
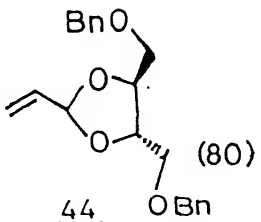
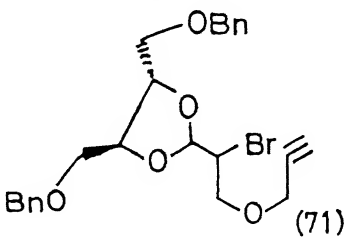
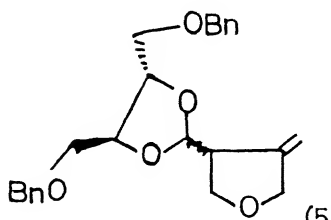
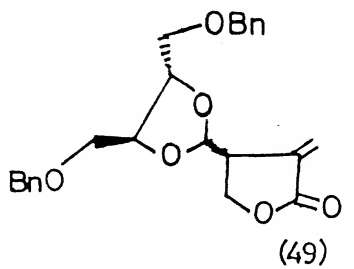
The spectral data

> 10°C to obtain compounds 45 and 46 respectively in good yields.

These structures were confirmed by their spectral data. nus, compound 45 had in its ^{1}H NMR spectrum peaks at δ 2.30-2.5 1H, t, -C≡CH), 3.34-3.68 (10H, m, 2X-CH_2OCH_3), 3.76-4.14 (3H, m, ethines, -CHBr), 4.17-4.34 (2H, d, -OCH_2-C≡C-), 5.10-5.18 (1H, d, H(O-)(O-)) and its mass spectrum indicated the molecular ion peak ery weakly at 322 corresponding to its molecular weight. imilarly compound 46 showed the expected spectral haracteristics. Compound 45 and 46 were subjected to radical yclisation with tributyltin hydride and a catalytic amount of IBN in benzene at 80°C for 2 hrs to obtain cyclic ethers 47 and 48 in 50% and 48% yield respectively. These cyclic ethers 47 and 48 were oxidised with CrO_3-Py reagent system to obtain α-methylene-γ-butyro lactones 49 and 50 in moderate yields (cf. Table 1). The lactone 49 exhibited IR peaks at 1740 cm^{-1} for lactone, and ^{1}H NMR values indicated at δ 2.8-2.9 (1H, m, br, -CH-C=C-), 3.35-3.65 (4H, m, 2X-CH_2O-), 3.9-4.2 (4H, m, -CH_2O-, methines), 4.5-4.7 (4H, s, PhCH_2OX2), 5.1-5.6 (3H, m, olefinic, -CH(O-)(O-)).

Unfortunately, high resolution ^{1}H NMR spectra (400 MHz) of compounds 49 and 50 in the presence of Eu(hfc)$_3$ once again indicated that the diastereoselectivity of these compounds was not high (only 4% in both the cases). Due to the poor selectivity obtained for lactones 37, 38, 49 and 50 attempts were not made to convert them into known compounds to find out the absolute configuration.


+ MeOH
NH4NO3
CH(OMe)3
OMe
OMe
39
MeO2C
CO2Me
OH
OH
40
PTSA
Benzene
80°C
CO2Me
CO2Me
41
LiAlH4
THF
HO
HO
42
NaH/THF
MeI or BnBr
OR
OR
R = – Me 43
R = – CH2Ph 44
OH
NBS
0–10°C
OR
Br
OR
R = – CH3 45
R = – CH2Ph 46
TBTH
AIBn
OR
OR
R = – CH3 47
R = – CH2Ph 48
CrO3–Py/DCM
OR
RO
R = – CH3 49
R = – CH2Ph 50

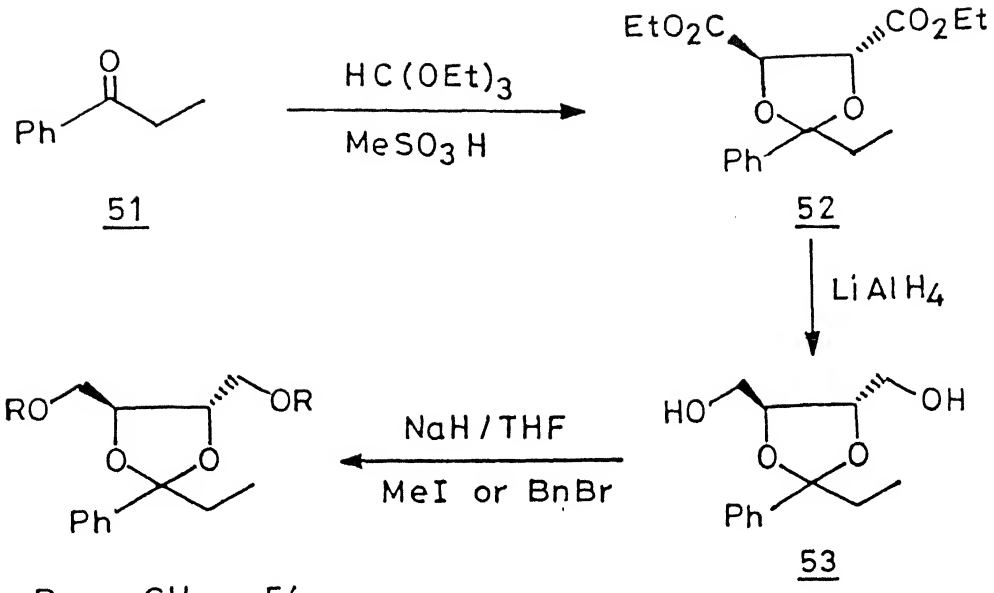
Entry	Olefin (% of yield)	Bromopropargylated acetal (% of yield)	Cyclised Product (% of yield)	α-methylene-γ-butyro lactones (% of yield)
(1)	 (50) 31	 (96) 33	 (60) 35	 (70) 37
(2)	 (65) 32	 (70) 34	 (65) 36	 (60) 38
(3)	 (82) 43	 (78) 45	 (54) 47	 (50) 49
(4)	 (80) 44	 (71) 46	 (50) 48	 (49) 50

In order to further investigate the effect of chiral acetals on intermolecular radical reactions involving carbon-carbon bond formation, we have undertaken α-bromo propiophenone acetal as the probe. All the starting materials were prepared according to a literature procedure[10]. Propiophenone 51 was acetalised with diethyl tartarate in the presence of methane sulphonic acid as a catalyst. The resulting compound 52 exhibited a strong IR absorption at 1720 cm^{-1} and ^1H NMR values were δ 0.85-1.51 (9H, m, $-CH_3X3$), 1.68-2.17 (2H, q, $-C\underline{H}_2CH_3$), 3.70-4.51 (4H, m, $-\overset{O}{\overset{\|}{C}}-O-CH_2-X2$), 4.68-4.8 (2H, s, methines), 7.17-7.85 (5H, m, aromatic). Propiophenone acetal 52 upon reduction with $LiAlH_4$ gave the diol 53 which upon methylation gave dimethylated acetal 54 and upon benzylation, gave dibenzylated ether 55 in very good yields. The two acetals 54 and 55 exhibited expected spectral characteristics for the structures assigned to them. All the three acetals 52, 54, and 55 were brominated with bromine in CCl_4 at 0^oC to room temperature to get α-bromo propiophenone acetals 56, 57, and 58 respectively, This procedure was the same as that adopted by Giordano et al.[10].

In order to find out the effect of chiral acetals on radical reactions these bromo acetals 56, 57, and 58 were allylated using allyl tributyltin (prepared from tributyltin chloride and allyl magnesium bromide) to obtain α-allylated acetals 59, 60, and 61 respectively. All these allylated products showed satisfactory spectral analysis. For example, compound 59 showed ^1H NMR signals at δ 0.8-1.8 (10H, m, $3X-CH_3$, $-\underset{|}{\overset{|}{C}}H$), 2.1-2.4 (2H, m, allylic), 3.7-4.1 (4H, m, $2X-OCH_2-$), 4.6-4.8 (2H, m, methines), 5.1-5.34

(1H, m, olefinic), 5.4-6.0 (2H, m, olefinic), 7.1-7.8 (5H, m, aromatic). Compound 60 has ^{1}H NMR signals at 0.8-1.6 (4H, m, $-CH_3$, $-C\underline{H}CH_3$), 2.1-2.3 (2H, m, allylic, $-CH_2-$), 3.22-3.52 (6H, 2s, $2X-OCH_3$), 3.51-3.88 (4H, m, $-CH_2O-X2$), 3.9-4.06 (2H, m, methines), 7.17-7.6 (5H, m, aromatic). Mass spectrum indicated the molecular ion peak at 306 corresponding to its molecular weight. Similarly, compound 61 showed ^{1}H NMR values at δ 0.8-0.9 (3H, d, $-\underset{|}{C}H-C\underline{H}_3$), 1.1-1.3 (1H, m, $-C\underline{H}-CH_3$), 2.1-2.3 (2H, m, allylic), 3.3-4.1 (6H, m, $2X-CH_2O-$, methines), 4.3-4.68 (4H, d, $PhC\underline{H}_2O-X2$), 4.9-5.9 (3H, m, olefinic), 7.1-7.8 (15H, m, aromatic). All these allylated acetals 59, 60, and 61 were hydrolysed under standard conditions to get α-allyl propiophenones 62A, 62B, and 62C respectively. The IR spectrum of compound 62A showed absorption at 1710 cm^{-1} and ^{1}H NMR indicated values at δ 0.9-1.5 (3H, t, $-CH_3$), 2.08-2.78 (2H, m, $-CH_2-$), 3.34-3.68 (1H, m, $-\overset{O}{\overset{\|}{C}}-CH-$), 4.8-6.17 (3H, m, olefinic), 7.17-8.34 (5H, m, aromatic) and mass spectrum indicated molecular ion peak at 174 corresponding to its molecular weight. Its specific rotation value was found to be $[\alpha]_D^{25} = +1^\circ$. Other two compounds 62B and 62C showed same spectral properties as 62A with specific rotation values as +0.5 and +1°. High resolution ^{1}H NMR analysis indicated that once again the enatioselectivities were not high and further attempts were not made to find out the stereochemistry of the carbon atom at the chiral centre.

In conclusion, it could be stated that both intramolecular and intermolecular radical cyclisations were not highly selective using chiral acetals that we studied and atleast under present reaction conditions.

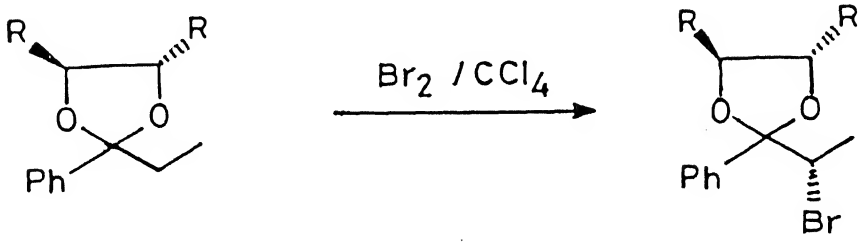


51 52 53

R = $-CH_3$ 54

R = $-CH_2Ph$ 55

SCHEME - 9



R = $-CO_2Et$ 52

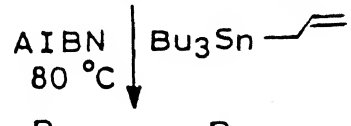
R = $-CH_2OMe$ 54

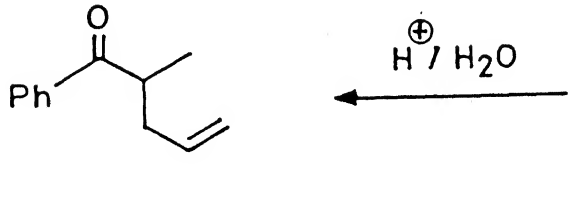
R = $-CH_2OPh$ 55

R = $-CO_2Et$ 56

R = $-CH_2OMe$ 57

R = $-CH_2OPh$ 58





62A (CO_2Et)

62B ($-CH_2OMe$)

62C ($-CH_2OPh$)

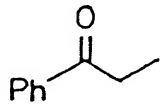
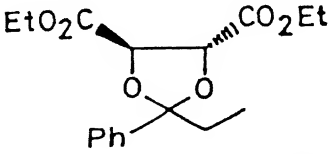
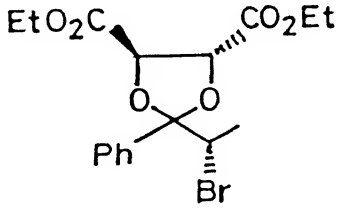
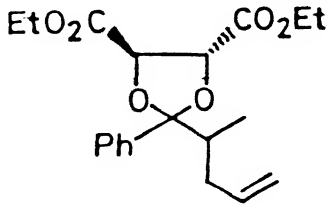
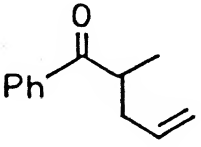
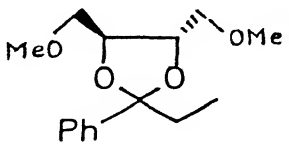
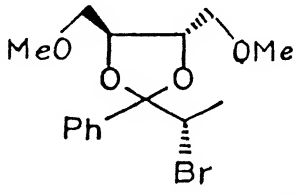
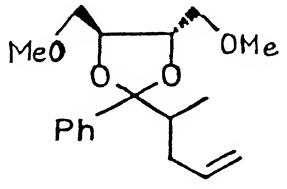
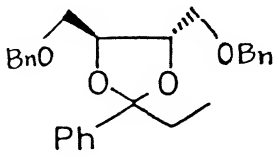
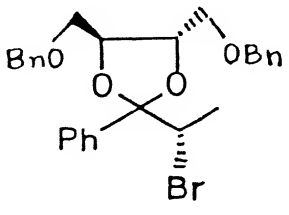
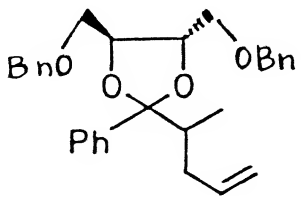
R = $-CO_2Et$ 59

R = $-CH_2OMe$ 60

R = $-CH_2OPh$ 61

SCHEME - 10

TABLE 2

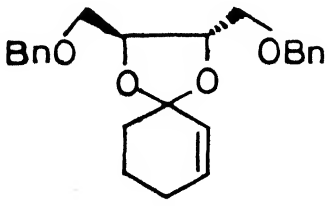
Entry	Substrate	Acetal (% of Yield)	Bromoacetal (% of yield)	Allylatedacetal (% of yield)	allyl propiophe (% of yield)
1	 51	 (52 (80)	 56 (90)	 59 (56)	 62A $-CO_2Et$ 62B $-OMe$ 62C $-OBn$
		 54 (86)	 57 (90)	 60 (50)	
		 55 (80)	 58 (30)	 61 (49)	

I.B.3 EXPERIMENTAL

General

All the solvents and reagents were purified according to the procedure followed in the Section I.A.3. Tributyltinchloride and propiophenone were obtained from E. Merck and were used as received. Tributyltinhydride was made by reducing tributyltin chloride with $LiAlH_4$.

Preparation of Olefinic Acetal 32



The olefinic acetal 32 was made according to the procedure followed for the compound 99 (cf. Section I.A.3).

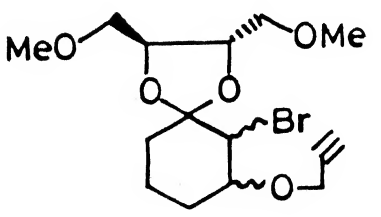
Yield : 66%

IR Spectrum (neat) ν_{max} : 3030, 1640 (C=C) cm^{-1}.

^1H NMR (CCl_4) : δ 1.8-2.3 (6H, m, aliphatic), 3.7-3.9 (4H, d, 2X-CH_2O-, J = 2.5 Hz), 4.1-4.25 (2H, m, methines), 4.5-4.85 (4H, s, $PhCH_2O$-X2), 5.6-6.2 (2H, m, olefinic), 7.2-7.5 (10H, m, aromatic).

Mass sepctrum (m/z) : 380 (M^+)

Preparation of Compound 33



To a solution of 31 (684 mg, 3 mmol) in 5 ml of anhydrous propargyl alcohol was added N-bromosuccinimide (669 mg, 3.75 mmol) in portions at $0^{o}C$. The reaction mixture was then stirred at $0\text{-}10^{o}C$ for 2 hrs. After removing excess of the alcohol at reduced pressure, the reaction mixture was quenched with saturated $NaHCO_3$ solution (10 ml) followed by extraction of the product in to ether (3x15 ml). The combined ether extracts were washed with water (20 ml) and brine (20 ml) and dried over anhydrous sodium sulphate. Removal of the solvent at the rotary evaporator gave a crude product which was purified by column chromatography (eluent 10% EA+PE) to afford 33 as a thick oil.

Yield = 1.050 gms, 96%

IR spectrum (neat) ν_{max} : 3280 (-C≡C-H), 2105 (-C≡C-) cm^{-1}.

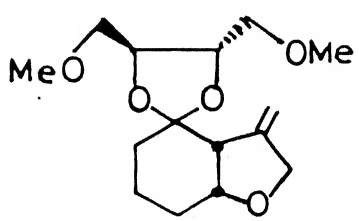
^1H NMR spectrum (CCl_4) : δ 1.3-2.03 (6H, m, 3X-CH_2-), 2.43 (1H, t, -C≡CH, J = 2 Hz), 3.3-3.67 (10H, m, containing a 6H, s at δ 3.4, 2X-CH_2-OCH_3), 3.8-4.43 (4H, m, H-C-O-, -CHBr and methines) and 4.47 (2H, t, -OCH_2-C≡CH, J = 2 Hz).

Mass spectrum m/z : 362 (weak M^+).

Anal. Calcd. for $C_{15}H_{23}BrO_5$: C, 49.6; H, 6.38.

Found : C, 49.41; H, 6.27%

Preparation of Compound 35



A mixture of 33 (364 mg, 1 mmol), freshly prepared and distilled tributyltinhydride (380 mg, 1.30 mmol) and

2,2'-azobisisobutyronitrile (25 mg, 0.15 mmol) in 5 ml of dry benzene was heated under reflux for 4h in a dry nitrogen atmosphere. After cooling, benzene was removed under vacuum and the crude product was purified by column chromatography to obtain 35 as a clear oil.

Yield : 170 mg, 60%

IR (neat) ν_{max} : 1650 (C≡C) cm^{-1}.

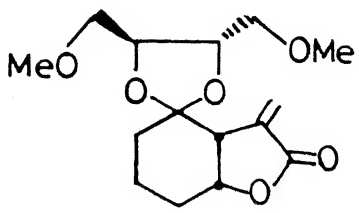
^1H NMR (CCl_4) : δ 1.35-2.0 (6H, m, 3X-CH_2-), 2.5-2.8 (1H, m, -CH-C=), 3.3-3.6 (10H, m, containing a 6H, s at δ 3.33, 2X-CH_2OCH_3), 3.75-4.27 (5H, m, -$CHOCH_2$C= and methines), 4.7-4.9 (1H, m, olefinic) and 5.0-5.23 (1H, m, olefinic).

Mass spectrum m/z : 289 (M^+). ? 284

Anal. Calcd. for $C_{15}H_{24}O_5$: C, 63.86; H, 8.51

Found : C, 63.4; H, 8.41%.

Oxidation of Compound 35



Chromiumtrioxide (400 mg, 4 mmol) was added to a solution of dry pyridine (780 mg, 9.8 mmol) in 4 ml of dry dichloromethane at 15-20°C and the resulting solution was stirred at 25°C for 30 minutes. To this was then added a solution of 35 (104 mg, 0.4 mmol) in 2 ml of dichloromethane and the reaction mixture was stirred at 30°C for 1.5 hr. It was treated with saturated $NaHCO_3$ solution (5 ml) and stirred for 30 minutes. During this time the solid materials went into solution with effervescence. The

organic layer was separated and the aqueous layer extracted with ether (3x10 ml). The combined organic layer was washed with water (2x10 ml) and brine (10 ml) and dried over anhydrous Na_2SO_4. Removal of the solvent gave a crude product which was purified by column chromatography to obtain the butyrolactone 37 as a viscous liquid.

Yield : 84 mg, 70%

IR spectrum (neat) ν_{max} : 3010 ($=CH_2$), 1760 (C=O, lactone) cm^{-1}.

^1H NMR ($CDCl_3$) : δ 1.4-2.0 (4H, m, 2X-CH_2-), 3.07 (1H, dd, -C<u>H</u>-C=CH_2, J = 2 Hz, 6 Hz), 3.3-3.6 (10H, m, containing a 6H, s at δ 3.33, 2X-CH_2OCH_3), 3.73-4.07 (2H, m, methines), 4.33-4.7 (1H, m, HC-O-), 5.67-5.87 (1H, m, olefinic) and 6.07 (1H, m, olefinic).

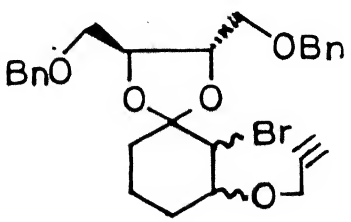
Mass spectrum m/z (rel. int.) : 298 (29, M^+) 115(100), 45(32).

Anal. Calcd. for $C_{15}H_{22}O_6$: C, 60.39; H, 7.43

Found : C, 60.51; H, 7.5%

Optical rotation : $[\alpha]_D^{25}$ = +6° (C1, CH_2Cl_2)

Preparation of Compound 34



To a stirred solution of 32 (760 mg, 2 mmol) in 4 ml of anhydrous propargyl alcohol was added N-Bromosuccinimide (442 mg, 2.5 mmol) portionwise and stirred at 0°C for one hour, followed by stirring at 10°C for one hour. Reaction was quenched with saturated $NaHCO_3$ (5 ml) and extracted with dichloromethane (3x15 ml). The combined dichloromethane layer was washed with water (25

ml) and brine solution (15 ml) and dried over anhydrous Na_2SO_4. Concentration and purification by column chromatography (eluent : 3% EA+PE) furnished pure 34 as a thick oil.

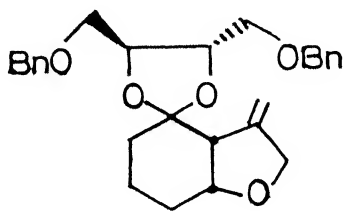
Yield : 0.719 gms, 70%.

IR (neat) : 3280, -C≡C-H), 2100 (-C≡C-) cm^{-1}.

^1H NMR ($CDCl_3$, 80 MHz) : 1.3-1.9 (6H, m, aliphatic), 2.45 (1H, t, -C≡C-H, J = 2 Hz), 3.65-3.7 (4H, d, 2X-CH_2O-), 3.95 (1H, d, HC(-O-)), 4.1 (1H, d, -CHBr, J = 2 Hz), 4.4 (2H, t, -OCH_2-C≡C-, J = 2.5 Hz), 4.45-4.70 (4H, d, PhCH_2O-X2), 7.2-7.5 (10H, m, aromatic).

Mass spectrum m/z : 514 (M^+)

Preparation of Compound 36



Compound 34 (514 mg, 1 mmol), n-tributyltinhydride (380 mg, 1.3 mmol), 2,2'-Azobisiosbutyronitrile (25 mg, 0.15 mmol) in 5 ml of benzene was heated under reflux for 4 hr. It was further processed as in the case of 35 and purified by column chromatography to obtain 36 as viscous liquid.

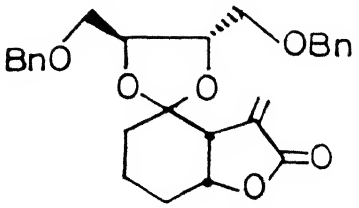
Yield : 287 mg, 65%.

IR (neat) : 1650 cm^{-1} (-C≡C-)

^1H NMR (CCl_4) 60 MHz : 1.17-1.85 (6H, m, aliphatic), 2.5-2.8 (1H, m, -CH-C=), 3.4-3.68 (4H, m, -CH_2-O-X2), 3.85-4.0 (3H, m, -CH_2O-CH-), 4.08-4.25 (2H, m, methines), 4.35-4.52 (4H, s, PhCH_2O-X2), 4.7-4.85 (1H, m, olefinic), 5.0-5.19 (1H, m, olefinic), 7.0-7.35 (10H, m, aromatic).

Optical Rotation : $[\alpha]_D^{25}$ = +18° (C1, CH_2Cl_2)

Preparation of Compound 38



Oxidation of the bicyclic ether (217 mg, 0.5 mmol) was carried out with CrO_3-Py in the same manner as that described for compound 37.

Yield : 134 mg, 60%.

IR spectrum (neat) ν_{max} : 1760 cm^{-1}.

^1H NMR ($CDCl_3$) : δ 1.17-1.85 (6H, m, aliphatic), 2.9-3.1 (1H, m, -CH-C=), 3.52-3.70 (4H, d, 2X-CH_2O-, J = 4 Hz), 3.85-4.10 (3H, m, HC-O-, methines), 4.35-4.6 (4H, s, $PhCH_2O$-X2), 5.6-5.87 (1H, m, olefinic), 6.04-6.17 (1H, m, olefinic), 7.04-7.39 (10H, m, aromatic).

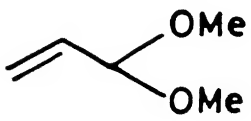
Mass spectrum m/z : 450 (M^+)

Anal. Calcd. for $C_{27}H_{30}O_6$: C,72.0; H,6.66

found C,69.4; H, 6.12 %

Optical Rotation : $[\alpha]_D^{25}$ = +14° (C1, CH_2Cl_2)

Preparation of Acrolein Dimethylacetal 39



To a solution of freshly distilled acrylaldehyde (10 gms, 178.5 mmol), trimethylorthoformate (22.7 gms, 213.6 mmol) in MeOH (11.42 gms, 357 mmol) was added hot solution of NH_4NO_3 (1.42 gms, 17.85

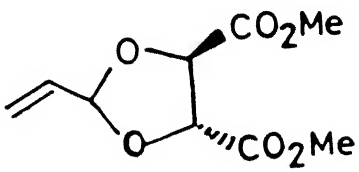
mmol) dissolved in 5 ml of MeOH and the mixture was stirred at room temperature for 12 hrs. Na_2CO_3 (10 gms) was added to the resulting dark brown colour solution and the reaction mixture was distilled to collect the pure compound boiling at 90°C.

Yield : 15.29 gms, 84%.

IR spectrum (neat) ν_{max} : 1620 cm^{-1}.

^1H NMR spectrum ($CDCl_3$, 60 MHz) : δ 3.08-3.35 (6H, s, 2X-OMe), 4.6-4.85 (1H, t, -C<u>H</u>$<^{OMe}_{OMe}$), 5.05-6.08 (3H, m, olefinic).

Preparation of Compound <u>41</u>



Acrolein dimethyl acetal <u>39</u> (2 gms, 19.6 mmol), dimethyl tartrate <u>40</u> (3.49 gms, 19.6 mmol), p-toluenesulphonic acid (337 mg, 1.96 mmol) were dissolved in 25 ml of dry benzene and heated at 80°C for 2 hrs, during which methanol was removed azeotropically with benzene at 58°C. Reaction mixture was quenched with saturated $NaHCO_3$ solution (5 ml) diluted with 25 ml of water and extracted with ether (3x25 ml). Combined ethereal layer was washed with brine (15 ml) and dried over anhydrous Na_2SO_4. Evaporation of organic layer at the rotary evaporator and purification by column chromatography (eluent : 10% EA+PE) yielded the pure product <u>41</u> as viscous liquid.

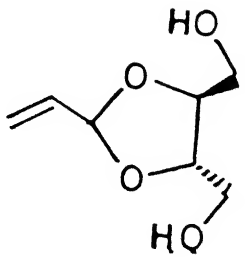
Yield : 2.11 gms, 50%.

IR spectrum (neat) ν_{max} : 1720 cm^{-1} (broad).

^1H NMR spectrum (CCl_4, 60 MHz) : δ 3.70-3.85 (6H, s, 2X-OCH_3),

4.51-4.8 (2H, dd, methines, J = 2.5 Hz, 4 Hz), 5.17-6.08 (4H, m, olefinic, -CH<O-/O->),

Reduction of Compound 41



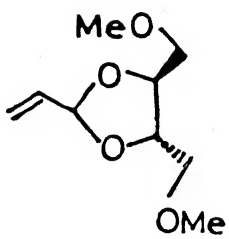
To a suspension of $LiAlH_4$ (720 mg, 20 mmol) in THF (25 ml), was added olefinic acetal 41 (1.08 gms, 5 mmol) in 10 ml of THF dropwise at 0^oC. After that it was refluxed for 4 hrs and the reaction mixture was cooled in an ice bath. Ethyl acetate (5 ml) and water (5 ml) was added to quench the reaction. It was filtered through a pad of celite and thoroughly extracted with ethyl acetate (50 ml). Removal of solvent gave the crude product 42 which was used as such for the next reaction.

Yield : 0.64 gms, 80%

IR spectrum (neat) ν_{max} : 3650-3400, 1610 cm^{-1}.

^1H NMR spectrum (CCl_4) : δ 2.1-2.4 (2H, br m, -OHX2), 3.3-3.68 (4H, m, $2X\text{-}OCH_2\text{-}$), 3.9-4.12 (2H, m, methines), 4.9-6.02 (4H, m, HC<O-/O->,olefinic).

Preparation of Compound 43



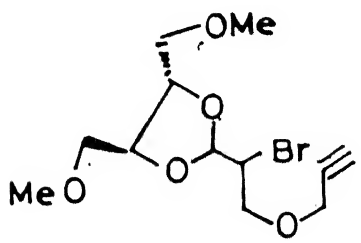
The olefinic diol 42 (800 mg, 5 mmol) in 5 ml of THF was added dropwise at $0^{o}C$ to a suspension of sodium hydride (300 mg, 10 mmol, 50% suspension in mineral oil) in 4 ml of THF. The reaction mixture was stirred for 30 minutes and MeI (1.69 gms, 12 mmol) was added dropwise to it and further stirred for 2 hrs. THF was removed under vacuum and water (15 ml) was added and extracted with ether (3x20 ml). Combined ethereal layer was washed with brine (15 ml). Evaporation at the rotary evaporator followed by purification by column chromatography yielded pure 43 as a mobile liquid.

Yield : 0.72 gms, 82%.

IR spectrum (neat) ν_{max} : 1610, 1020 cm^{-1}

^{1}H NMR spectrum ($CDCl_3$, 80 MHz) : δ 3.4-3.52 (6H, s, 2X-OMe), 3.6-3.68 (4H, d, $-O-CH_2-X2$, J = 3.75 Hz), 3.9-4.17 (2H, m, methines), 5.19-6.12 (4H, m, $HC<^{O-}_{O-}$, olefinic).

Preparation of Compound 45



To a solution of olefinic acetal 43 (940 mg, 5 mmol) in 3 ml of propargyl alcohol was added NBS (1.062 gms, 6 mmol) portionwise and further proceeded as mentioned for the compound 33. Purification by column chromatography (eluent 10:90 EA/PE) yielded the pure product 45 as viscous oil.

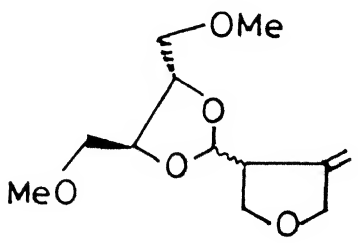
Yield : 1.25 gm, 78%.

IR spectrum (neat) ν_{max} : 3275, 2100 cm^{-1}.

^{1}H NMR spectrum (CCl_4, 60 MHz) : δ 2.30-2.51 (1H, t, -C≡C-H, J = 2 Hz), 3.34-3.68 (10H, m, $2XCH_2$-OCH_3), 3.76-4.14 (3H, m, -O-CH_2-, -CH-Br), 4.17-4.34 (2H, t, -OCH_2-C≡C-H), 5.10-5.18 (1H, d, $HC<^{O-}_{O-}$ J = 2.5 Hz).

Mass spectrum m/z : 322 (M^+)

Cyclisation of Compound 45



Compound 45 (322 mg, 1 mmol), n-tributyltinhydride (380 mg, 1.3 mmol), AIBN (25 mg, 0.15 mmol) in benzene were refluxed for 2 hrs. It was cooled and the solvent was removed in the vacuum to give the crude product which was purified by column chromatography (eluent : 15 EA+PE) to give 47 as pale yellow oil.

Yield : 0.131 gm, 54%

IR spectrum (neat) ν_{max} : 1650 cm^{-1}.

^{1}H NMR spectrum (CCl_4, 60 MHz) δ : 2.17-2.3 (1H, m, -CH-C=C-), 3.34-3.65 (10H, m, $2XCH_2OMe$), 3.68-4.08 (4H, m, $2X$-CH_2O), 4.17-4.38 (2H, m, methines), 4.85-4.9 (1H, d, $CH<^{O-}_{O-}$, J = 2 Hz), 5.08-5.17 (1H, m, olefinic), 5.51-5.65 (1H, m, olefinic).

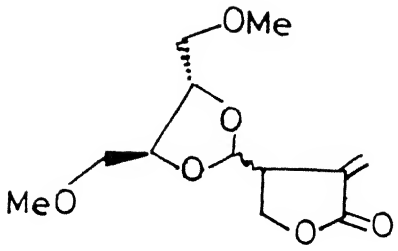
Mass spectrum m/z : 244 (M^+)

Anal. Calcd. for $C_{12}H_{20}O_5$: C,59.0; H,8.1

found C,59.6; H,8.2 %

Optical Rotation : $[\alpha]_D^{25}$ = +2.5° (C1, CH_2Cl_2).

Oxidation of Compound 47



Compound 47 was oxidised to α-methylene-γ-buturolactone according to the procedure mentioned for the compound 37 and purified by column chromatography (eluent : 7% EA+PE) to get 49 as a thick oil.

IR spectrum (neat) ν_{max} : 3010, 1760 cm^{-1}.

^1H NMR spectrum (CCl_4) : δ 2.1-2.3 (1H, m, -CH-C=C-), 3.4-3.7 (10H, m, 2X-CH_2OMe), 3.8-4.1 (4H, m, 2X-CH_2O-), 4.2-4.35 (2H, m, methines) 4.85-4.9 (1H, d, -CH$\langle^{O-}_{O-}$), 5.17-5.43 (1H, m, olefinic), 5.7-6.01 (1H, m, olefinic).

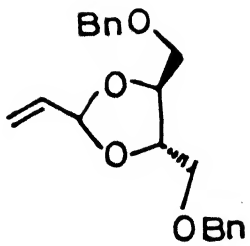
Mass spectrum m/z : 258 (M^+)

Anal. Calcd. for $C_{12}H_{16}O_6$: C,55.8; H,6.2

found C,56.1; H,6.4 %

Optical Rotation : $[\alpha]_D^{25}$ = +4° (C1, CH_2Cl_2)

Preparation of Compound 44



Olefinic diol 42 (800 mg, 5 mmol) in 5 ml THF was added to a suspension of sodium hydride (360 mg, 12 mmol) in mineral oil at 0°C and stirred for 30 minutes. Benzylbromide (1.87 gm, 11 mmol)

in 3 ml of THF was added to it and stirred for another 4 hrs. Further it was processed as in the case of compound 43 to obtain 44 as thick oil.

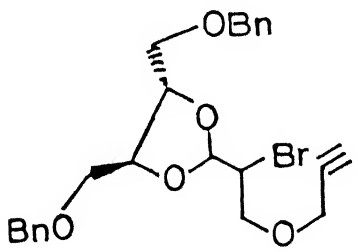
Yield : 1.36 gm, 80%.

IR spectrum (neat) ν_{max} : 1610, 1020, 960 cm^{-1}.

^1H NMR (CCl_4, 60 MHz) : δ 3.5-3.6 (4H, d, $-OCH_2-X2$, J = 4 Hz), 3.8-4.1 (2H, m, methines), 4.4-4.6 (4H, s, $PhCH_2O-X2$), 5.1-5.8 (4H, m, olefinic, $-CH<^{O-}_{O-}$), 7.08-7.34 (10H, m, aromatic).

Mass spectrum m/z : 258 (M^+)

Preparation of Compound 46



Olefinic acetal 44 (680 mg, 2 mmol), NBS (3.89 mg, 2.2 mmol), propargyl alcohol (2 ml). Procedure was same as that for 34.

Purification : Petroleum ether - Ethyl acetate

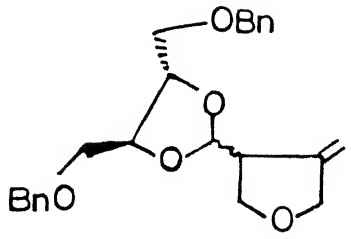
Yield : 0.673 gm, 71%.

IR spectrum (neat) ν_{max} : 3280, 2105 cm^{-1}.

^1H NMR (CCl_4, 60 MHz) : δ 2.1-2.3 (1H, t, $-C\equiv C-H$, J = 2 Hz), 3.17-3.65 (4H, m, $-OCH_2X2$), 3.7-4.1 (3H, m, methines, -CHBr), 4.4-4.6 (4H, s, $PhCH_2O-X2$), 4.9-5.1 (1H, d, $-CH<^{O-}_{O-}$), 7.17-7.4 (10H, m, aromatic).

Mass spectrum m/z : 474 (M^+)

Cyclisation of Compound 46



Compound 46 (474 mg, 1 mmol), n-tributyltinhydride (380 mg, 1.33 mmol), AIBN (25 mg, 0.15 mmol). Procedure same as that for 35.

Purification : Petroleum ether - Ethyl acetate

Yield : 198 mg, 50%

IR spectrum (neat) ν_{max} : 1650 cm^{-1}.

^1H NMR spectrum (CCl_4, 60 MHz) : δ 2.7-2.9 (1H, m, br, -CH-C=C-), 3.35-3.65 (4H, m, 2X-CH_2O-), 3.75-4.2 (6H, m, -CH_2O, -OCH_2-C=, methines), 4.5-4.7 (4H, s, $PhCH_2O$-X2), 4.9-5.35 (3H, m, olefinic, $-CH\begin{matrix}O-\\O-\end{matrix}$).

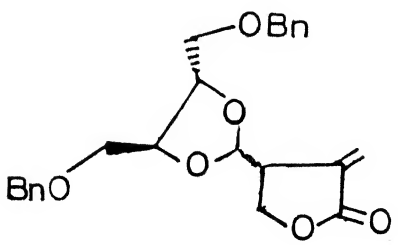
Mass spectrum m/z : 396 (M^+)

Anal. Calcd. for $C_{24}H_{28}O_5$: C,72.7; H,7.0

found C,71.9; H,6.8 %

Optical Rotation : $[\alpha]_D^{25}$ = +4° (C1, CH_2Cl_2)

Oxidation of Compound 48



Compound 48 (132 mg, 0.33 mmol), CrO_3 (133 mg, 1.3 mmol), pyridine (211 mg, 2.64 mmol). Procedure was same as that of 37.

Purification : Petroleum ether - Ethyl acetate

Yield : 71 mg, 50%.

IR spectrum (neat) ν_{max} : 3010, 1760 cm^{-1}.

^1H NMR spectrum (CCl_4, 60 MHz) : δ 2.8-2.9 (1H, m, br, -CH-C=C-), 3.35-3.65 (4H, m, 2X-CH_2O-), 3.9-4.2 (4H, m, -CH_2O, methines), 4.5-4.7 (4H, s, PhCH_2O-X2), 5.1-5.6 (3H, m, olefinic, -CH O O).

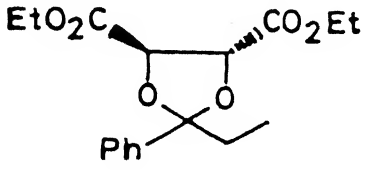
Mass spectrum m/z : 410 (M^+)

Anal. Calcd. for $C_{24}H_{26}O_6$: C,70.2; H,6.3

found C,70.1; H,6.1 %

Optical Rotation : $[\alpha]_D^{25}$ = +3°(C1, CH_2Cl_2)

Preparation of Propiophenone Diethyltartrateacetal 52



A solution of propiophenone (2 gms, 14.92 mmol), diethyl tartarate (6.14 gms, 29.89 mmol), triethyl orthoformate (4.41 gms, 27.84 mmol) was heated at 80°C and to that was added methane sulphonic acid (0.143 gm, 1.49 mmol) dropwise and heated further at the same temperature for two more hours. Saturated $NaHCO_3$ (5 ml solution) was added to the reaction mixture and diluted with water (20 ml). It was thoroughly extracted with dichloromethane (3x20 ml) and combined organic layers were washed with brine (25 ml) and dried over Na_2SO_4. Concentration at the reduced pressure followed by purification (5% EA+PE) gave the pure product 52 as a thick liquid.

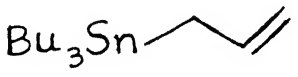
Yield : 3.84 gms, 80%.

IR spectrum (neat) ν_{max} : 1720 cm^{-1} (broad).

^1H NMR spectrum (CCl_4, 60 MHz) : δ 0.85-1.51 (9H, m, -CH_3X3),

1.68-2.17 (2H, q, $-CH_2CH_3$), 3.70-4.51 (4H, m, 2X-OCH_2-), 4.68-4.8 (2H, s, methines), 7.17-7.85 (5H, m, aromatic).

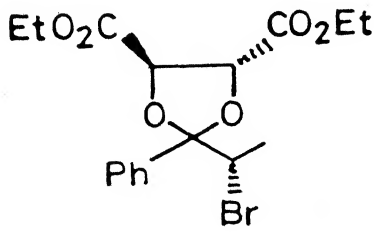
Preparation of Allyltributyltin



10 ml of anhydrous ether was added to a mixture of freshly activated magnesium turnings (348 mg, 12 mmol) and 10 mg of iodine at room temperature. To that was added allyl bromide (1.44 gm, 12 mmol) dissolved in 4 ml of ether dropwise at 10-15°C. After all the magnesium got homogenised, freshly distilled tributyl tin chloride (3.25 gm, 10 mmol) in 2 ml of ether was added to it at 0°C and stirred for 2 hr. Saturated NH_4Cl (5 ml) was added to it very slowly and was thoroughly extracted with 25 ml of water and ether (3x25 ml). Combined ethereal layers was washed with brine solution (25 ml) and dried over anhydrous Na_2SO_4. Ether was removed at rotary evaporator and the crude product was purified by column chromatography (eluent : petroleum ether).

Yield : 84%.

Bromination of Compound 52



Bromine (1.58 gm, 10 mml) in 5 ml of CCl_4 was added dropwise at

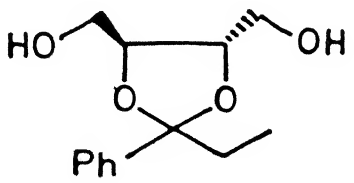
$15^{o}C$ to a stirred solution of propiophenone diethyl tartarate actal 56 (3.22 gms, 10 mmol) dissolved in 10 ml of CCl_4 and was stirred further for 2 hrs. Saturated $NaHCO_3$ (5 ml) was added to it and it was thoroughly extracted with dichloromethane (3x25 ml). Combined organic layers were washed with water (25 ml) and brine (20 ml). Dichloromethane was removed inthe vacuum and the crude product was purified by column chromatography (5% EA+PE) to give the pure product 56.

Yield : 3.6 gms, 90%.

IR spectrum (neat) ν_{max} : 1720 cm^{-1} (broad).

^1H NMR spectrum (CCl_4, 60 MHz) : δ 0.9-1.85 (9H, m, 3X-CH_3), 3.85-4.17 (5H, m, -CH_2OX2, -$\overset{|}{C}$H-Br), 4.70-5.0 (2H, dd, J = 6 Hz, 7 Hz), 7.20-7.84 (5H, m, aromatic).

Reduction of Compound 52



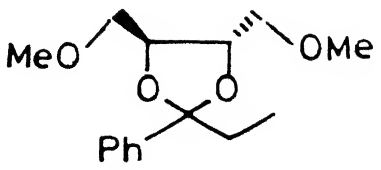
$LiAlH_4$ (1.080 gm, 30 mmol), propiophenone diethyltartarate acetal 52 (3.22 gm,10 mmol). Procedure was same as that of compound 42.

Yield : 0.938 gm, 78%.

IR spectrum (neat) ν_{max} : 3500-3350 cm^{-1}.

^1H NMR spectrum (CCl_4, 60 MHz) : δ 0.7-1.06 (3H, t, -CH_2-$\underline{CH}_3$, J = 6 Hz), 1.70-2.17 (2H, q, -$\underline{CH}_2$-CH_3), 2.35-2.75 (2H, m, br, -OHX2), 3.34-4.17 (6H, m, 2X-$\underline{CH}_2$OH, methines), 7.34-7.6 (5H, m, aromatic).

Preparation of Compound 54



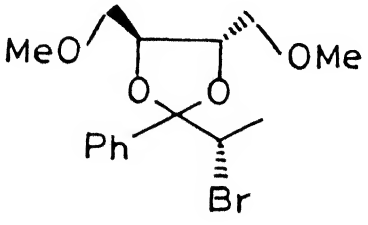
Diol 58 (1.190 gm, 5 mmol), NaH (360 mg, 12 mmol, 80% dispersion in mineral oil), MeI (1.692 gm, 12 mmol). Procedure was same as that of 43. Eluent : 7% EA+PE.

Yield : 1.14 gm, 86%.

IR spectrum (neat) ν_{max} : 1020, 960 cm^{-1}.

^1H NMR spectrum (CCl_4, 60 MHz) : δ 0.7-1.0 (3H, t, $-CH_3$, J = 7 Hz), 1.6-2.06 (2H, q, $-CH_2-CH_3$, J = 7 Hz), 3.17-3.28 (6H, s, $2X-OCH_3$), 3.34-3.42 (4H, s, $2X-CH_2O-$), 3.65-4.01 (2H, m, methines), 7.17-7.68 (5H, m, aromatic).

Bromination of Compound 54



Bromine (790 mg, 5 mmol), acetal 54 (1.33 gm, 5 mmol). Procedure was same as that for 56. Purification by column chromatography (eluent : 4%, EA+PE) gave pure 57.

Yield : 1.54 gm, 90%.

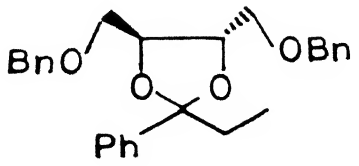
IR spectrum (neat) ν_{max} : 1020, 960 cm^{-1}.

^1H NMR spectrum (CCl_4, 60 MHz) : δ 1.4-1.68 (3H, d, $-CH_3$, J = 7 Hz), 3.25-3.6 (10H, m, $2XCH_2OCH_3$), 3.9-4.3 (3H, m, $-CHBr$,

methines), 7.19-7.7 (5H, m, aromatic).

Mass spectrum m/z : 344 (M^+)

Preparation of Compound 55



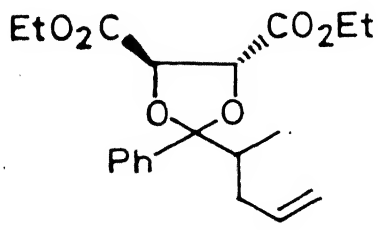
Diol 53 (1.190 gm, 5 mmol), NaH (360 mg, 12 mmol, 80% dispersion in mineral oil) and benzylbromide (2.040 gm, 12 mmol). Procedure was similar to that of 43. Purification (eluent 2% EA+PE).

Yield : 1.70 gm, 80%.

IR spectrum (neat) ν_{max} : 1170, 1020, 960 cm^{-1}.

^1H NMR spectrum (CCl_4, 60 MHz) : δ 0.7-1.0 (3H, t, $-CH_3$, J = 7 Hz), 1.6-2.01 (2H, q, $-CH_2-CH_3$, J = 7 Hz), 3.17-3.68 (4H, m, $-CH_2O$-X2), 3.85-4.11 (2H, m, methines), 4.35-4.6 (4H, 2s, $PhCH_2O$-X2), 7.17-7.63 (15H, m, aromatic).

Allylation of Compund 56



Bromoacetal 56 (400 mg, 1 mmol), allyl tributyl tin (496 mg, 1.5 mmol), AIBN (25 mg, 0.15 mmol) in dry benzene (10 ml) was heated at 80°C for 2 hrs. Solvent was removed in the vacuum and the crude product was purified by column chromatography (eluent : 3%

EA+PE) to get pure 59 as a viscous liquid.

Yield : 0.202 mg, 56%.

IR spectrum (neat) ν_{max} : 1650, 1725 (broad) cm^{-1}.

^1H NMR spectrum (CCl_4, 60 MHz) : δ 0.8-1.8 (10H, m, $3XCH_3$, -CH-CH_3), 2.1-2.4 (2H, m, allylic), 3.7-4.1 (4H, m, $2X-OCH_2-$), 4.6-4.8 (2H, m, methines), 5.1-5.34 (2H, m, olefinic), 5.4-6.0 (1H, m, olefinic), 7.1-7.8 (5H, m, aromatic).

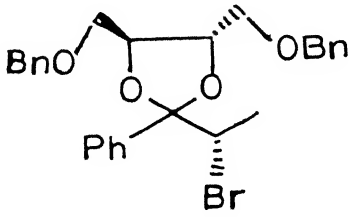
Mass spectrum m/z : 362 (M^+)

Anal. Calcd. for $C_{20}H_{26}O_6$: C,66.2; H,10.6

found C,65.8; H,10.8

Optical rotations : $[\alpha]_D^{25}$ = +8°(C1, CH_2Cl_2)

Bromination of Compound 55



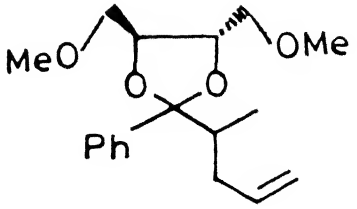
Bromine (790 mg, 5 mmol), acetal 55 (1.94 gm, 5 mmol). Procedure was similar to that of 56. Purification : 2% EA+PE.

Yield : 0.699 gm, 30%.

IR spectrum (neat) ν_{max} : 1610(w), 1170, 960 cm^{-1}.

^1H NMR spectrum (CCl_4, 60 MHz) : δ 1.1-1.5 (3H, d, -CH_3-CH-), 3.17-4.5 (7H, m, $2X-CH_2O-$, -CHBr, mehines), 5.15-5.30 (4H, d, $PhCH_2O-X2$), 7.1-8.3 (15H, m, aromatic).

Allylation of Compound 57



Bromoacetal 57 (344 mg, 1 mmol), allyltributyl tin (496 mg, 1.5 mmol), AIBN (25 mg, 0.15 mmol). Procedure was same as that of 59. Purification : 2% EA+PE.

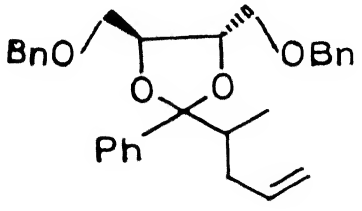
Yield : 153 mg, 50%.

IR spectrum (neat) ν_{max} : 1650, 1620, 1070, 960 cm^{-1}.

^1H NMR spectrum (CCl_4, 60 MHz) : δ 0.8-1.6 (4H, m, $-CH_3$, $-CH-CH_3$), 2.1-2.3 (2H, m, allyl $-CH_2-$), 3.2-3.52 (6H, 2s, $2X-OCH_3$), 3.51-3.88 (4H, m, $-CH_2O-X2$), 3.9-4.06 (2H, m, methines), 7.17-7.6 (5H, m, aromatic).

Optical rotation : $[\alpha]_D^{25}$ = +6.5°(C1, CH_2Cl_2)

Allylation of Compound 58



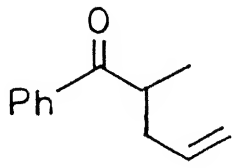
Bromoacetal (248 mg, 0.5 mmol), Allyl tributyl tin (331 mg, 1 mmol), AIBN (75 mg, 0.15 mmol). Procedure was same for that of 59. Purification : 2% EA+PE.

Yield : 0.112 mg, 49%.

IR spectrum (neat) ν_{max} : 1650, 1600, 1170, 960 cm^{-1}.

^1H NMR spectrum (CCl_4, 60 MHz) : δ 0.8-0.9 (3H, d, CH_3-CH-),

Hydrolysis of Compound 59



Acetal 59 (120 mg, 0.33 mmol), PTSA (30 mg, THF 2 ml), H_2O 1 ml were heated at 60°C for 10 hrs. Neutralized with a saturated $NaHCO_3$ (2 ml) and worked up with ether (3x15 ml). Ether layers were washed with 10 ml of saturated brine solution and dried over anhydrous sodium sulphate. Solvent was removed at the reduced pressure and the crude product was purified by column chromatography to get 62A. Eluent : Petroleum ether.

Yield : 43 mg, 75%.

IR spectrum (neat) : 1720, 1630 cm^{-1}.

^1H NMR spectrum (CCl_4, 60 MHz) : δ 0.9-1.5 (3H, d, -CH-C<u>H</u>$_3$, J = 7 Hz), 2.08-2.78 (2H, m, -CH_2-C=C-), 3.34-3.68 (1H, m, O=C-CH-), 5.0-5.34 (2H, m, olefinic), 5.4-5.9 (1H, m, olefinic), 7.17-8.34 (5H, m, aromatic).

Optical rotation : $[\alpha]_D^{25}$ = +1°(C1, CH_2Cl_2).

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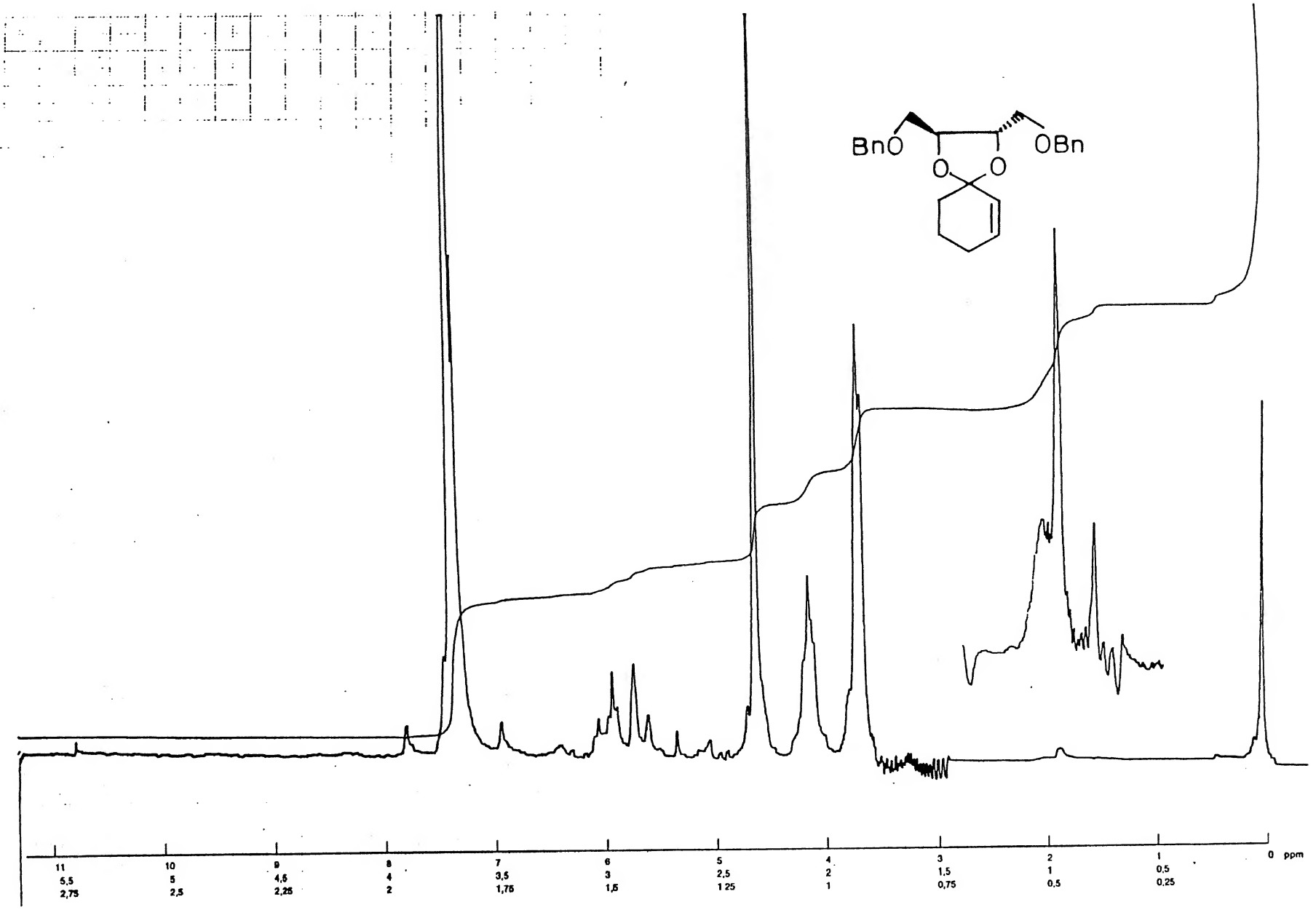
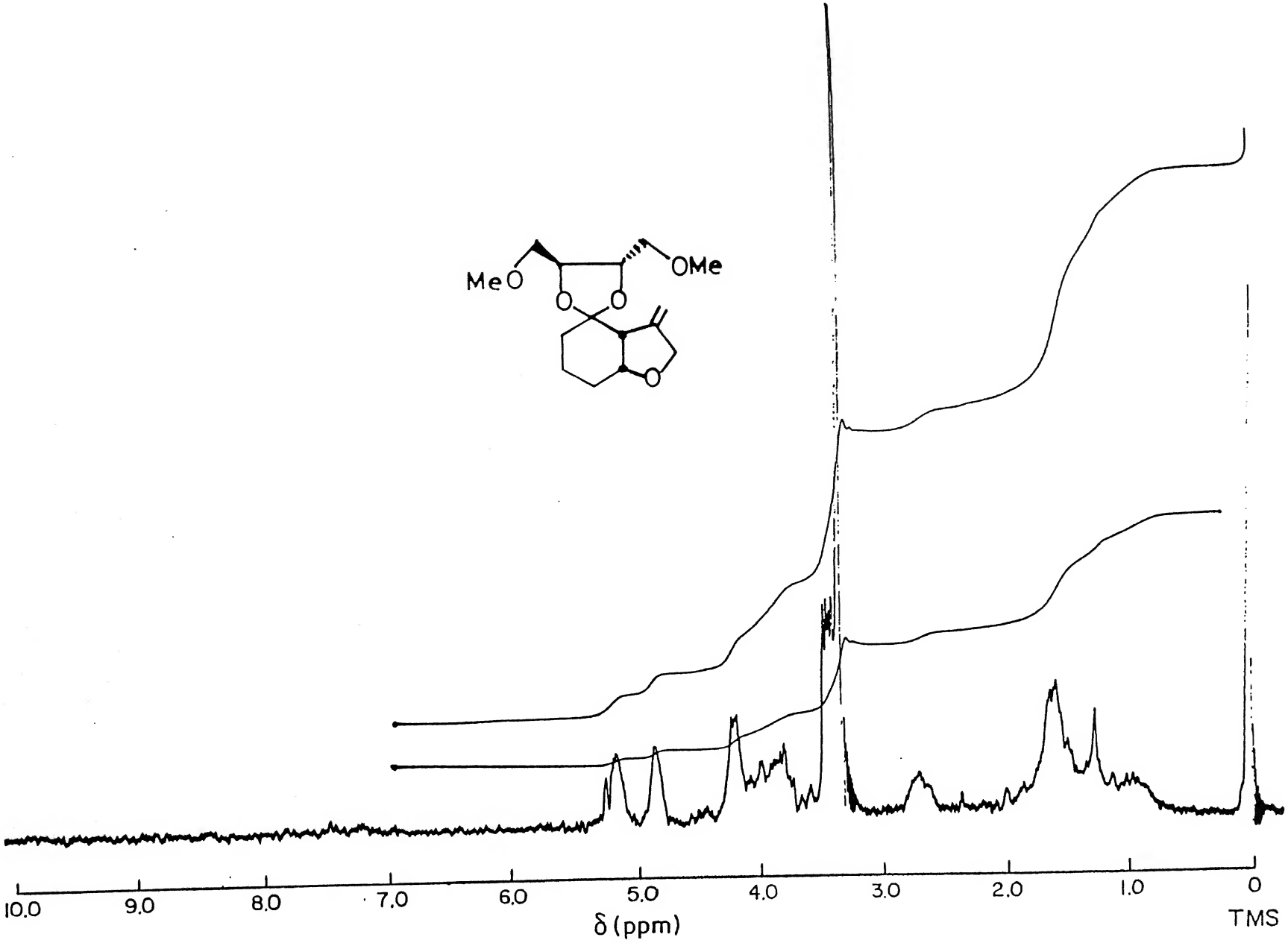
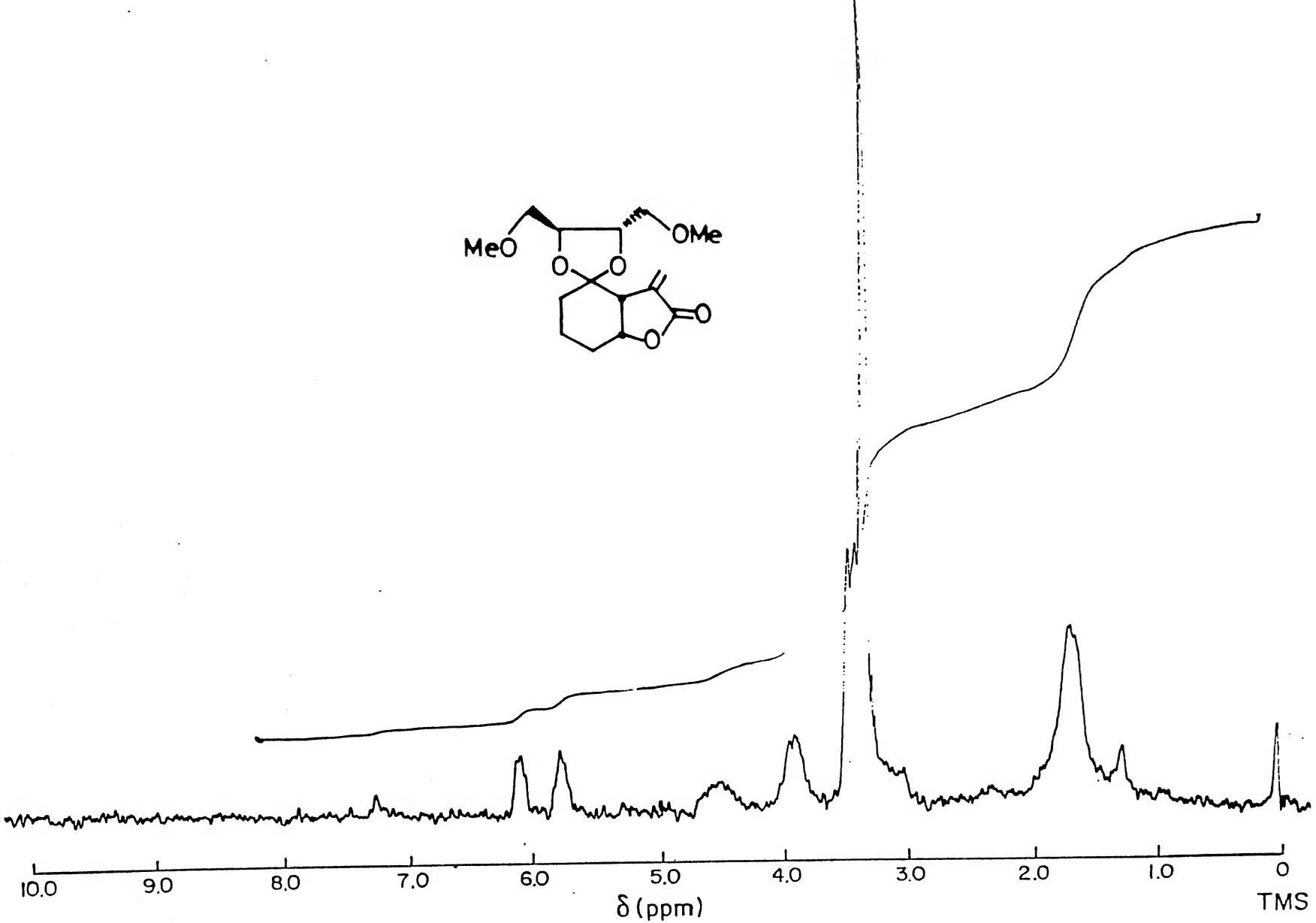


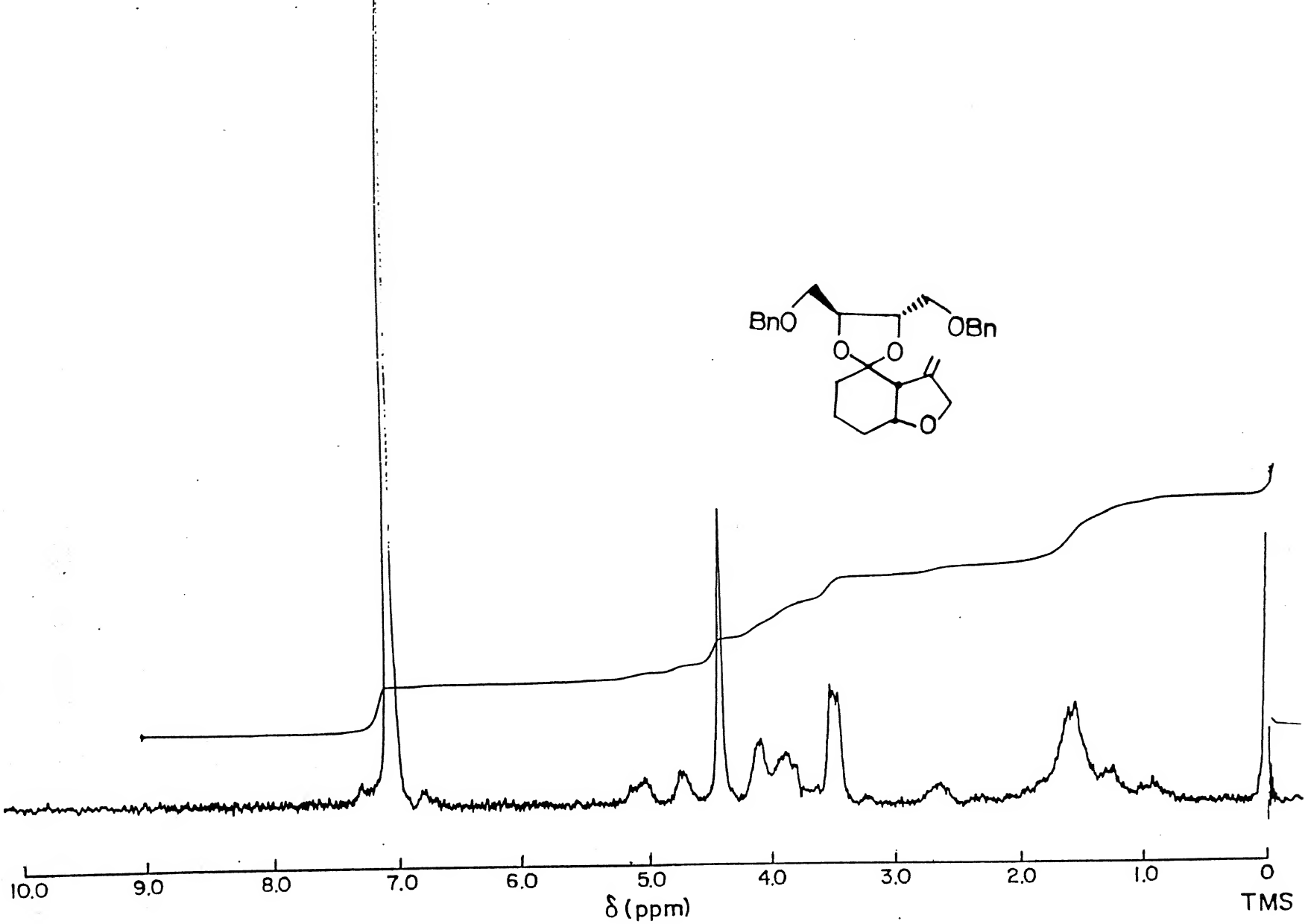
80 MHz ^{1}H NMR spectrum of the compound 32



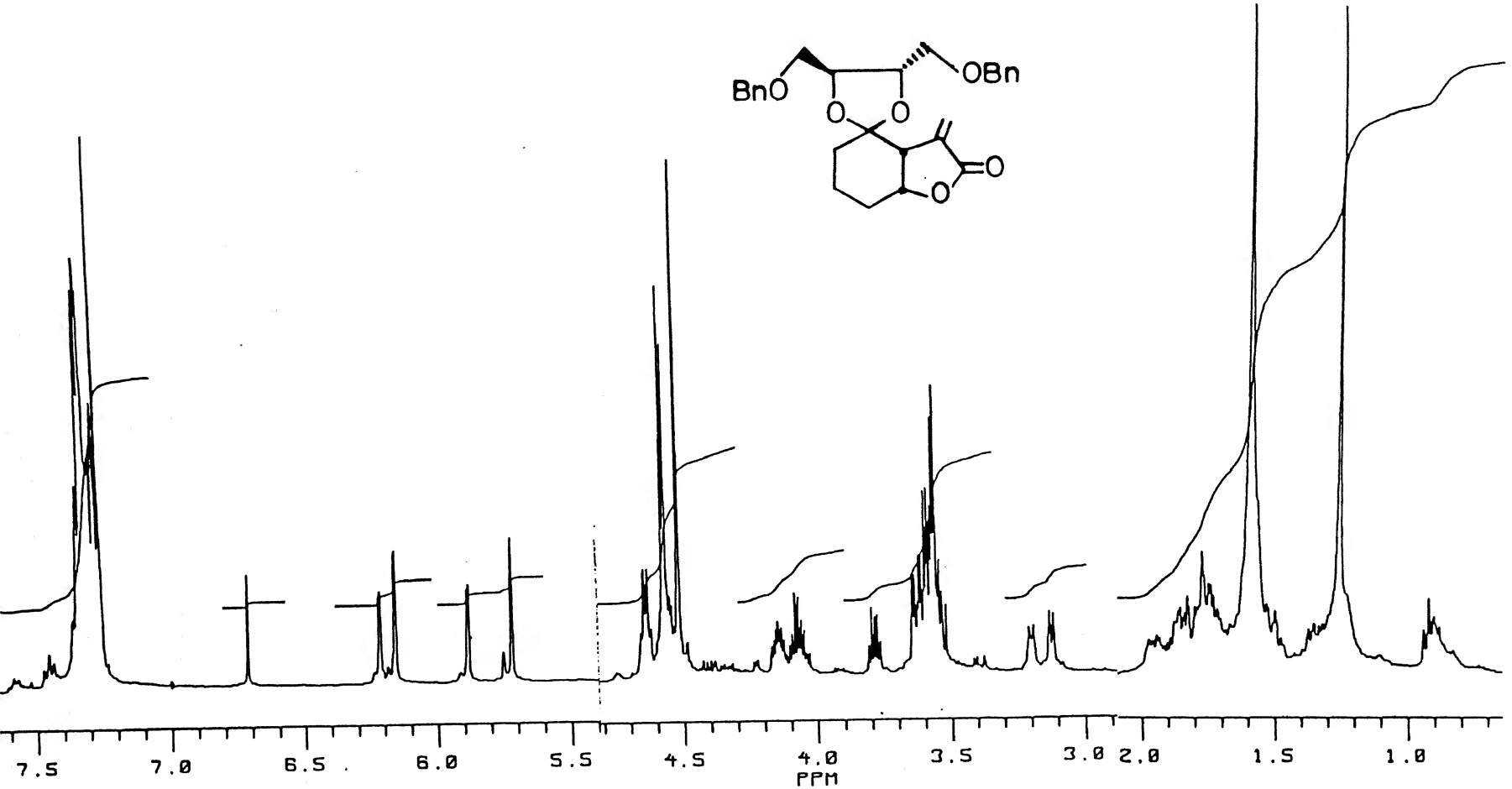
60 MHz ^{1}H NMR spectrum of the compound 35



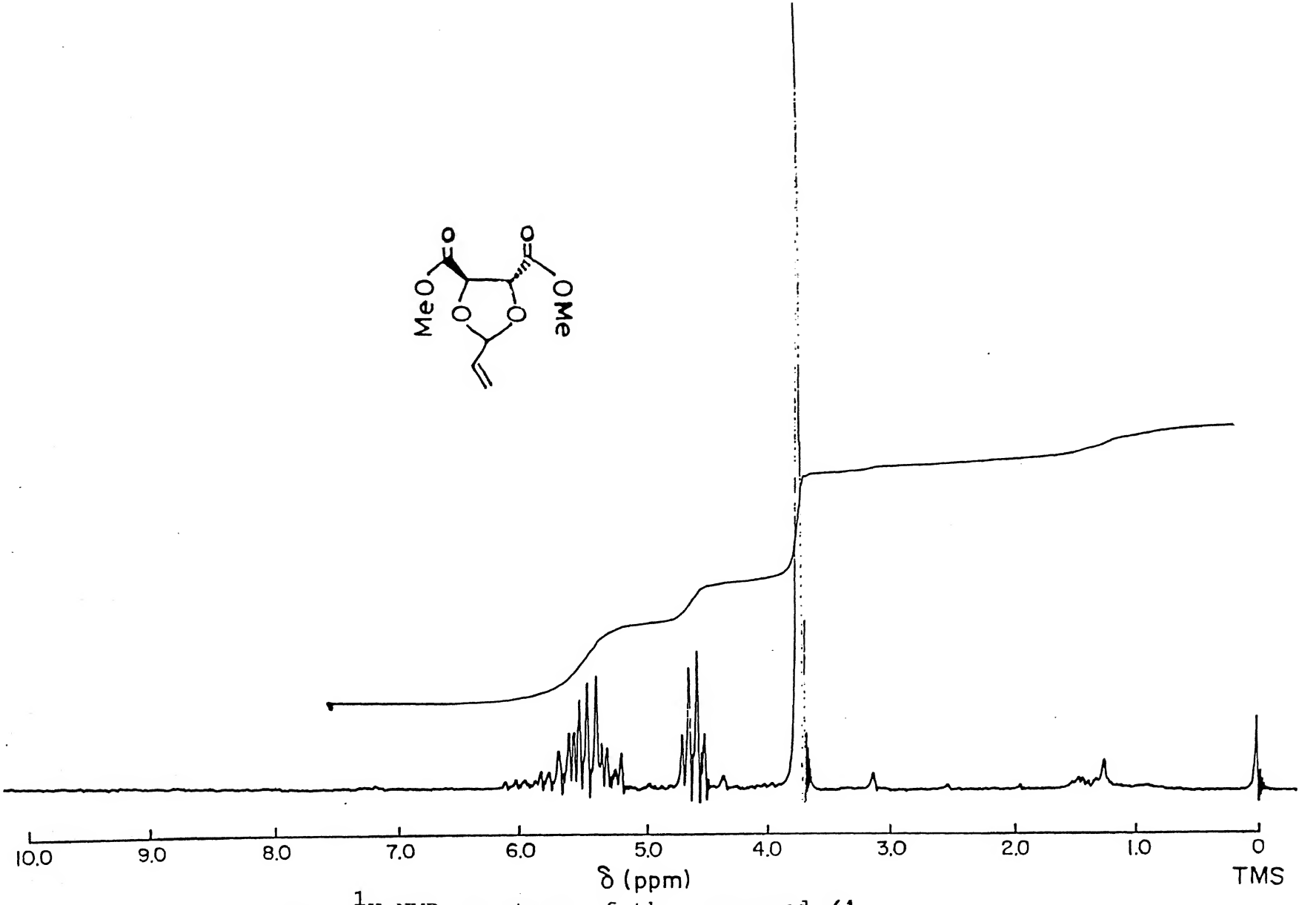
60 MHz ^{1}H NMR spectrum of the compound 37



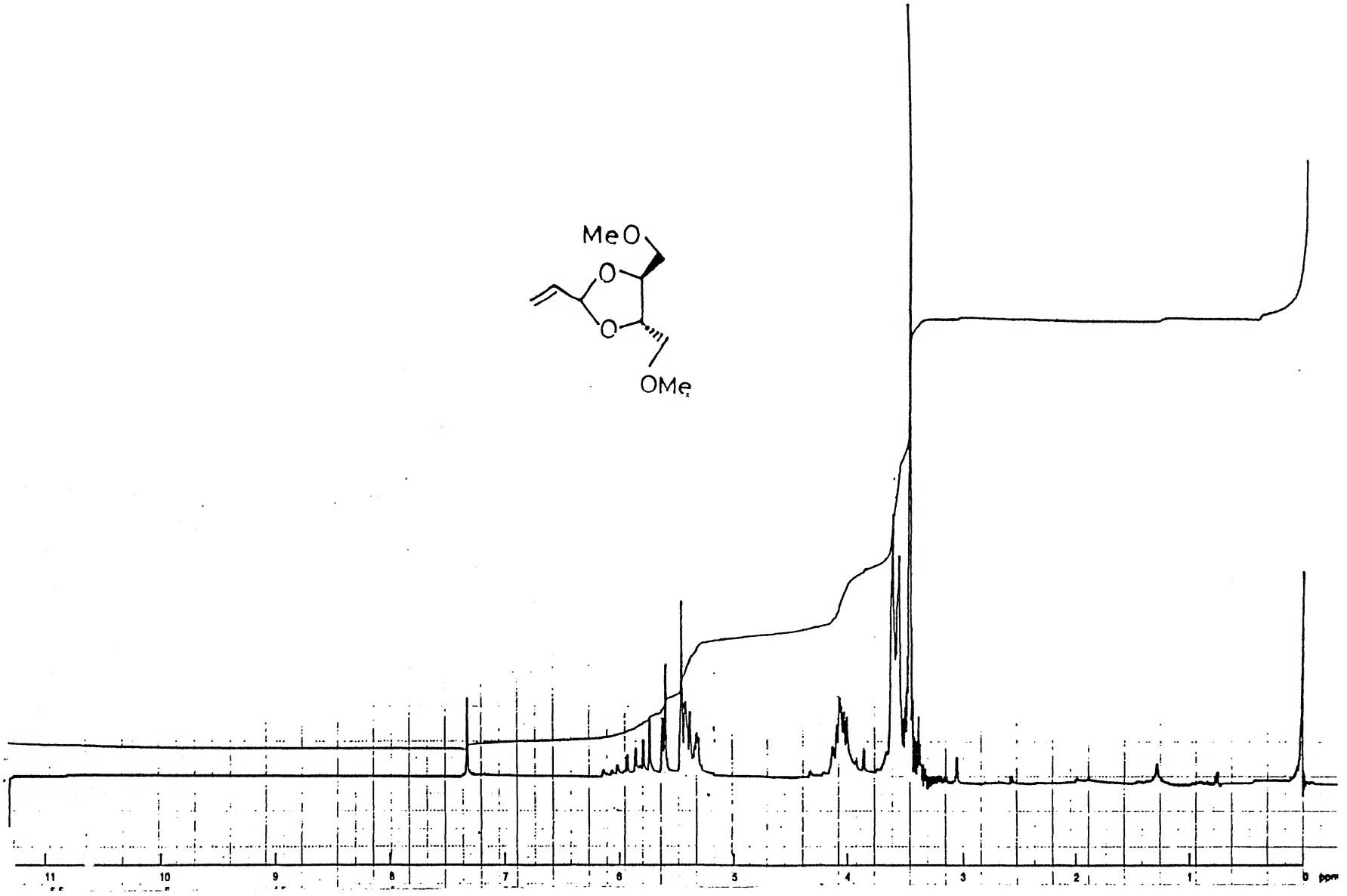
60 MHz ^{1}H NMR spectrum of the compound 36



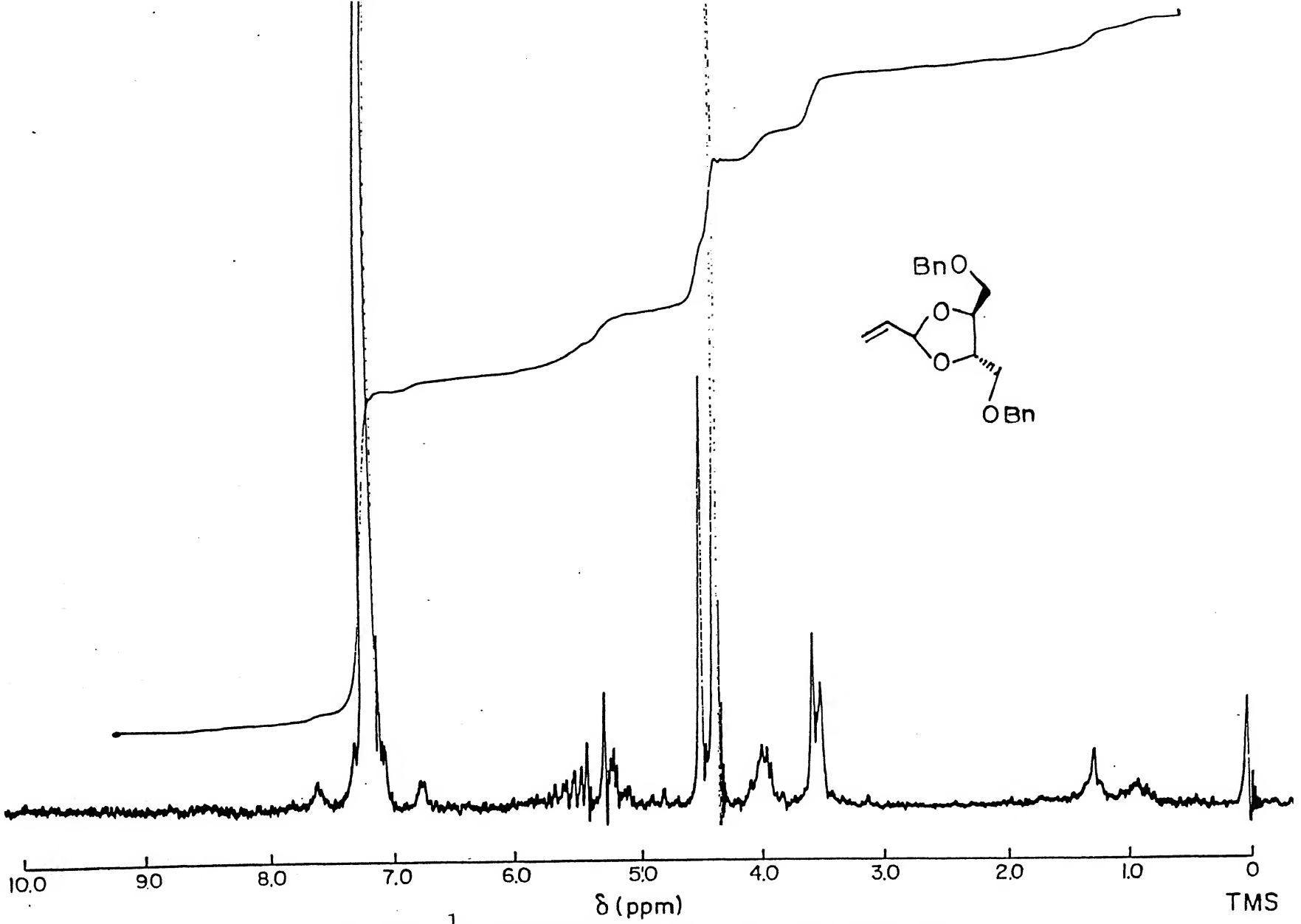
400 MHz ^{1}H NMR spectrum of the compound 36



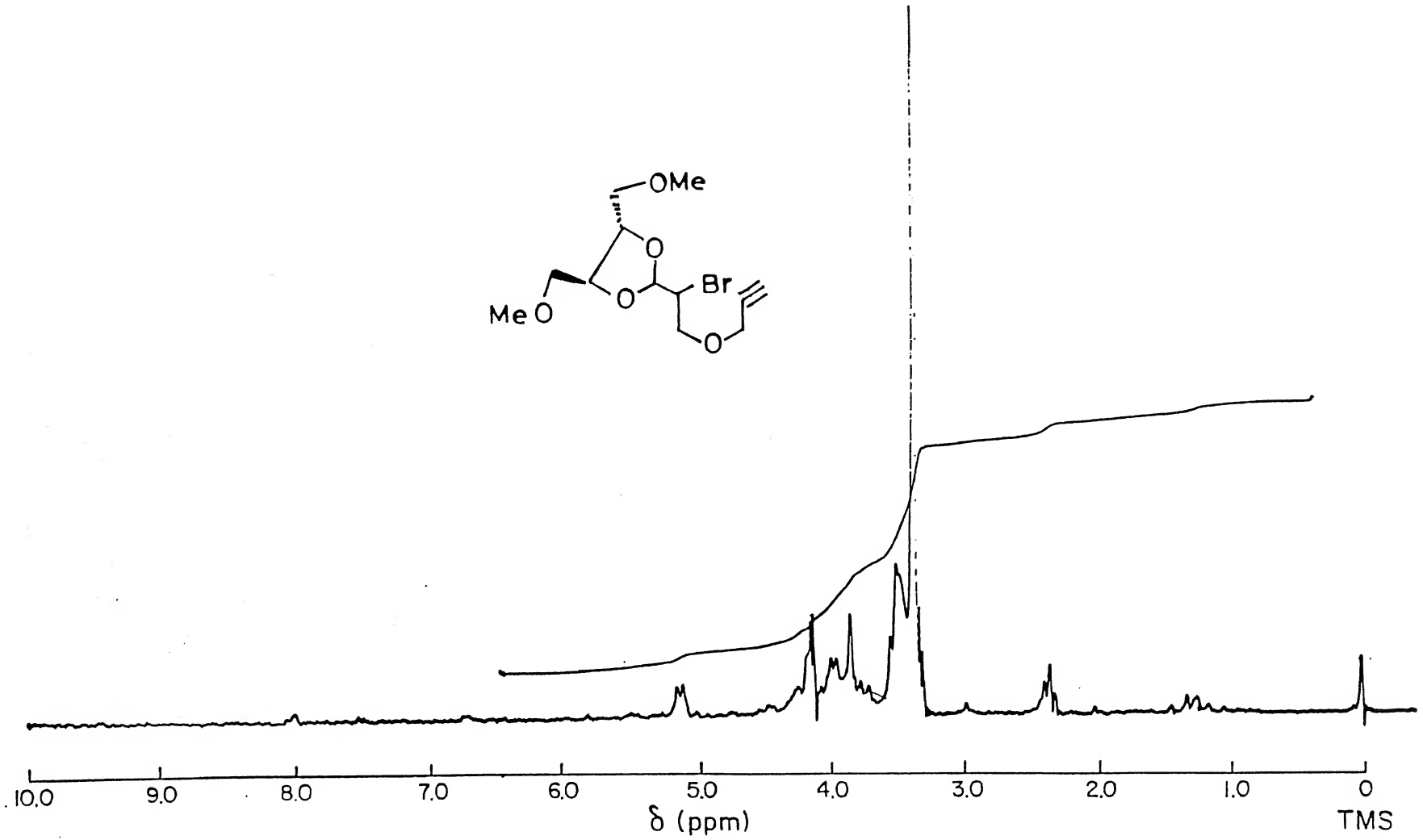
60 MHz ^{1}H NMR spectrum of the compound 41



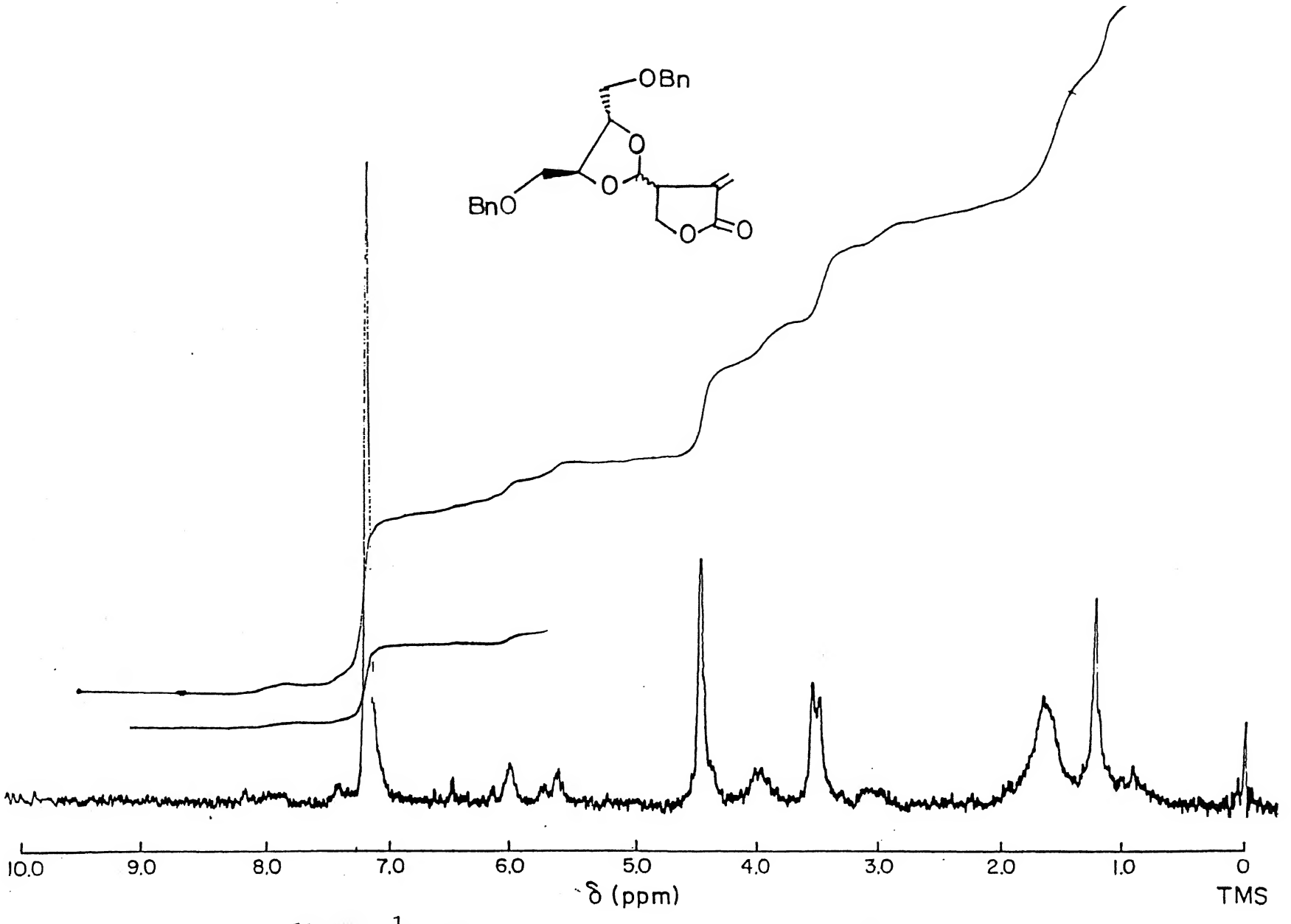
80 MHz ^{1}H NMR spectrum of the compound 43



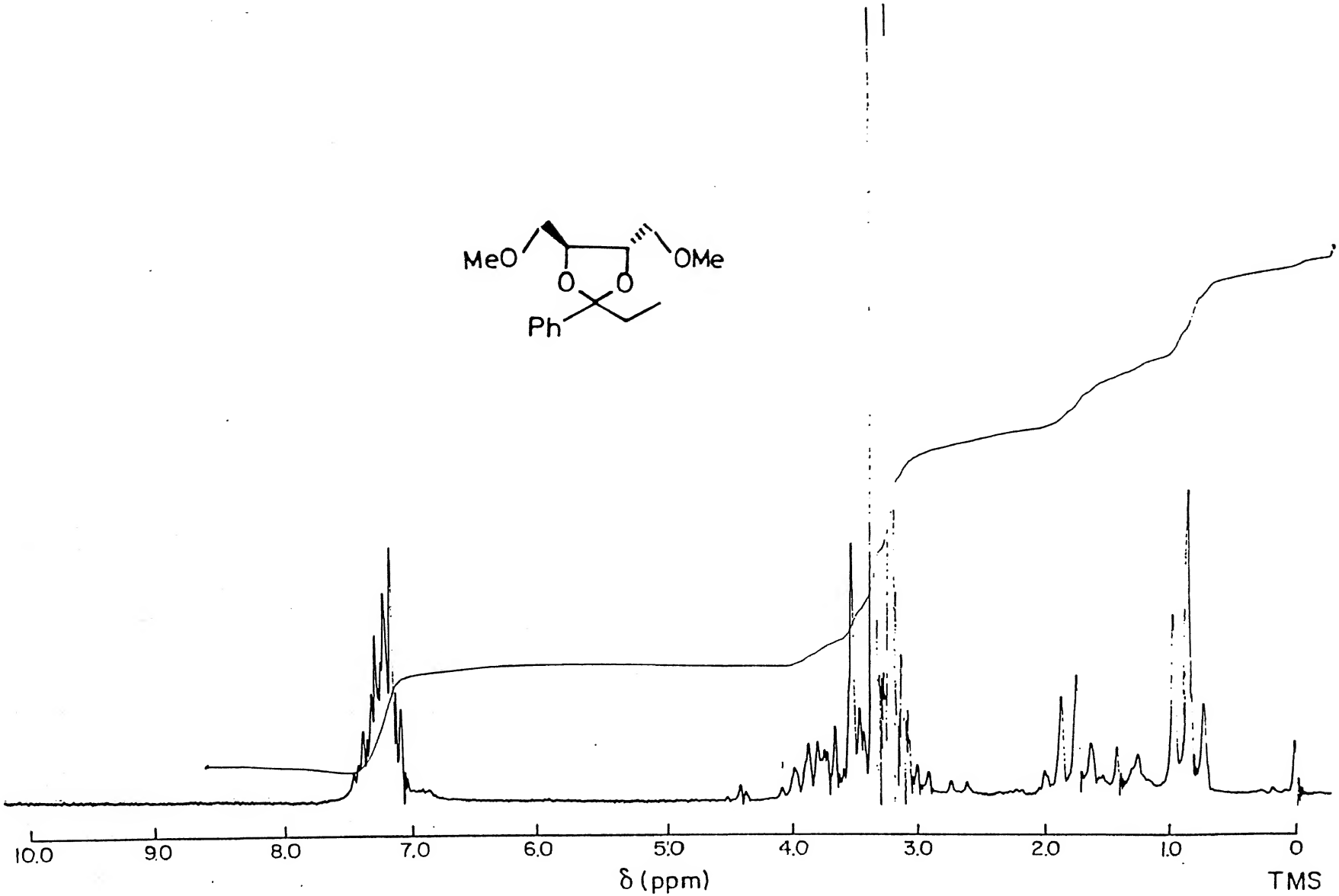
60 MHz ^{1}H NMR spectrum of the compound 44



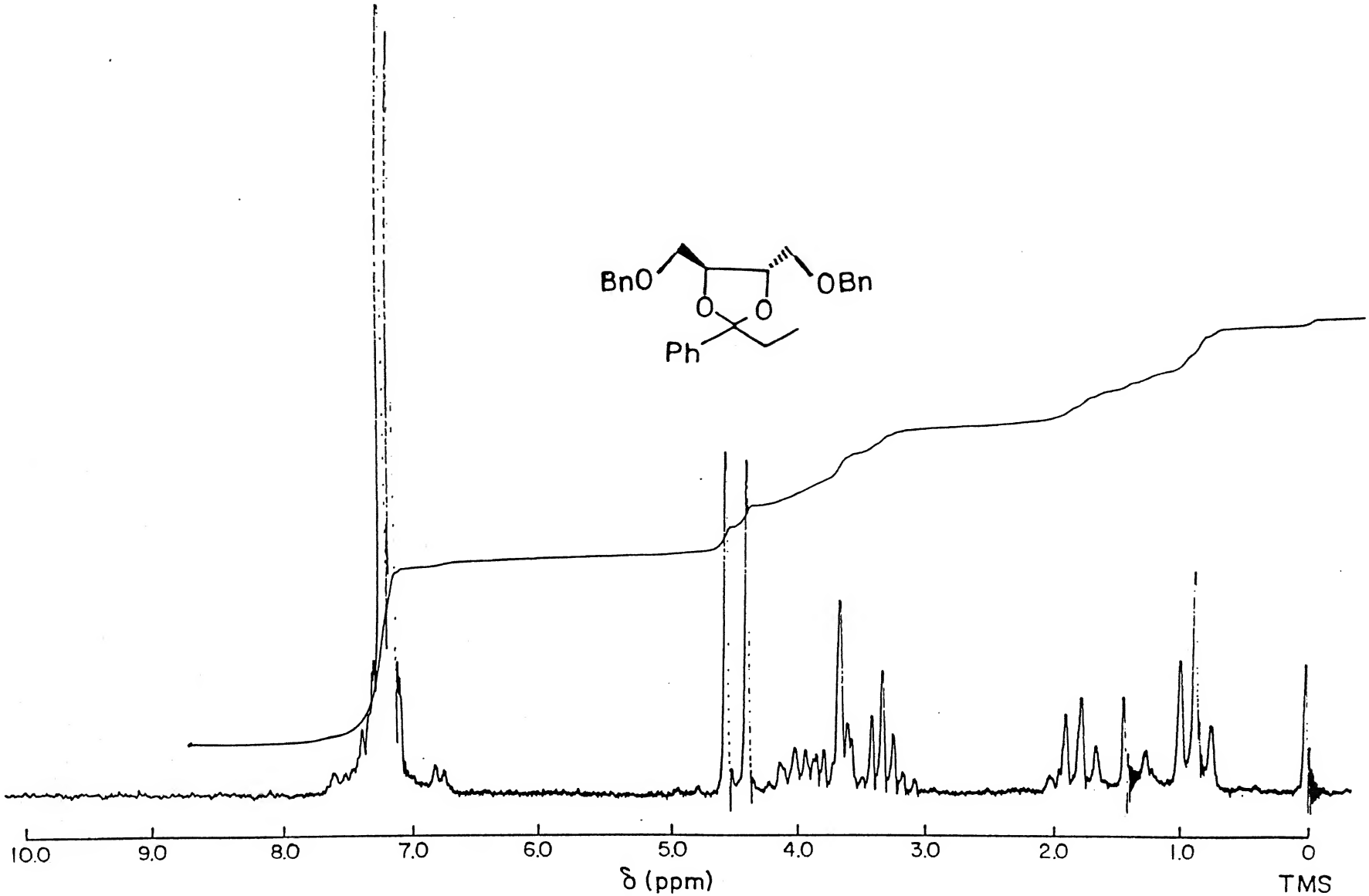
60 MHz ^{1}H NMR spectrum of the compound 45



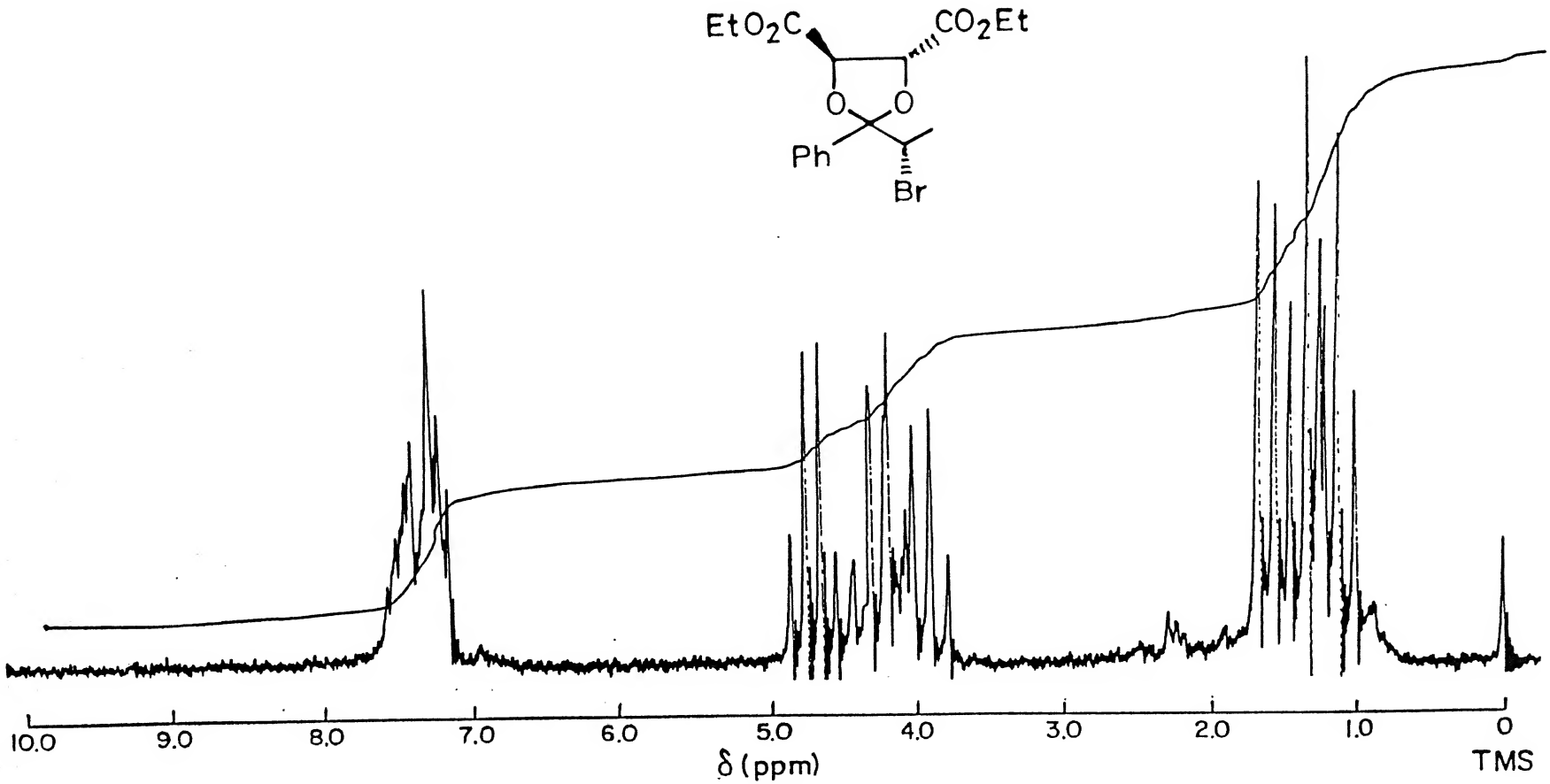
60 MHz ^{1}H NMR spectrum of the compound 50



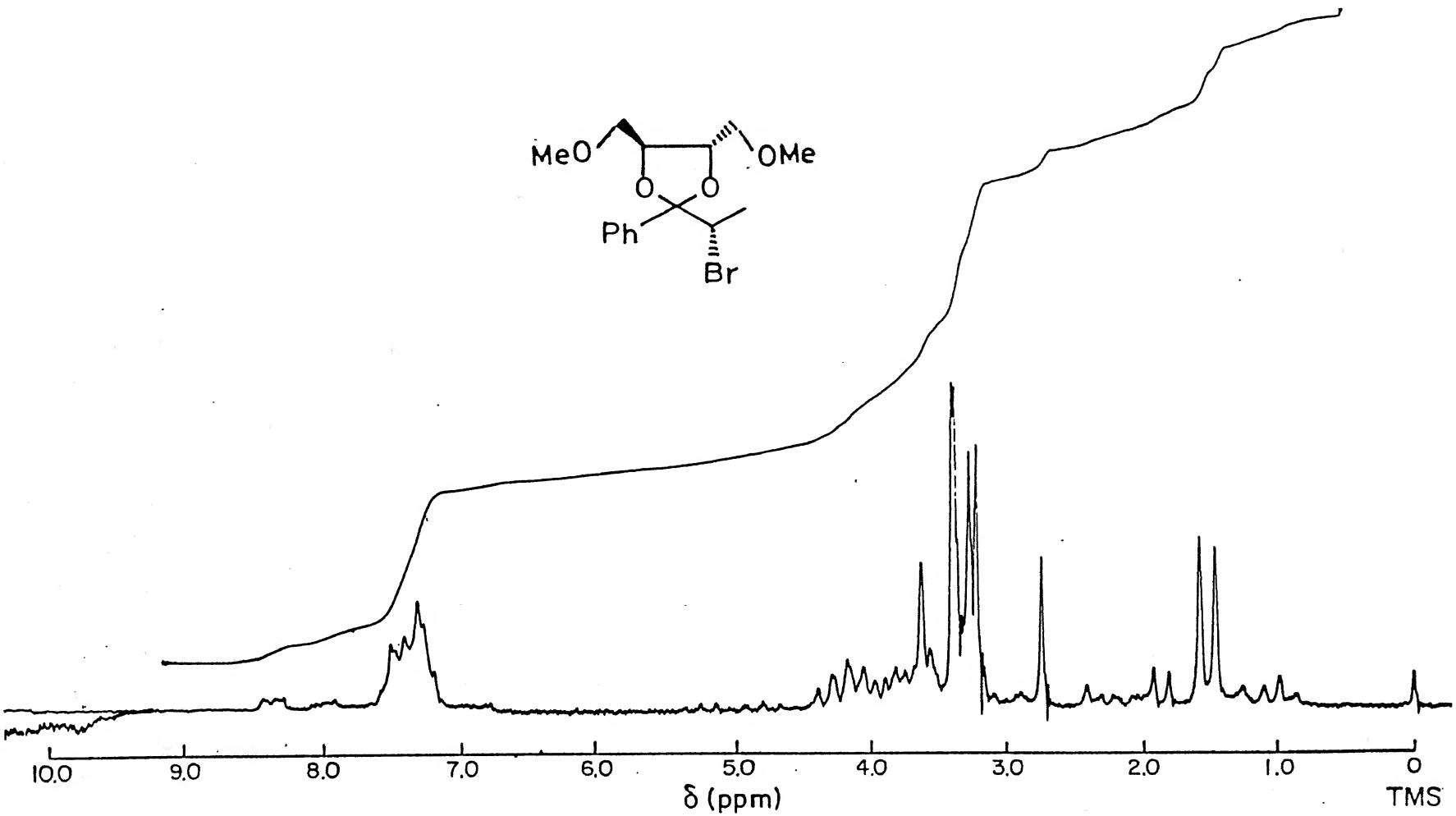
^{1}H NMR spectrum of the compound 54



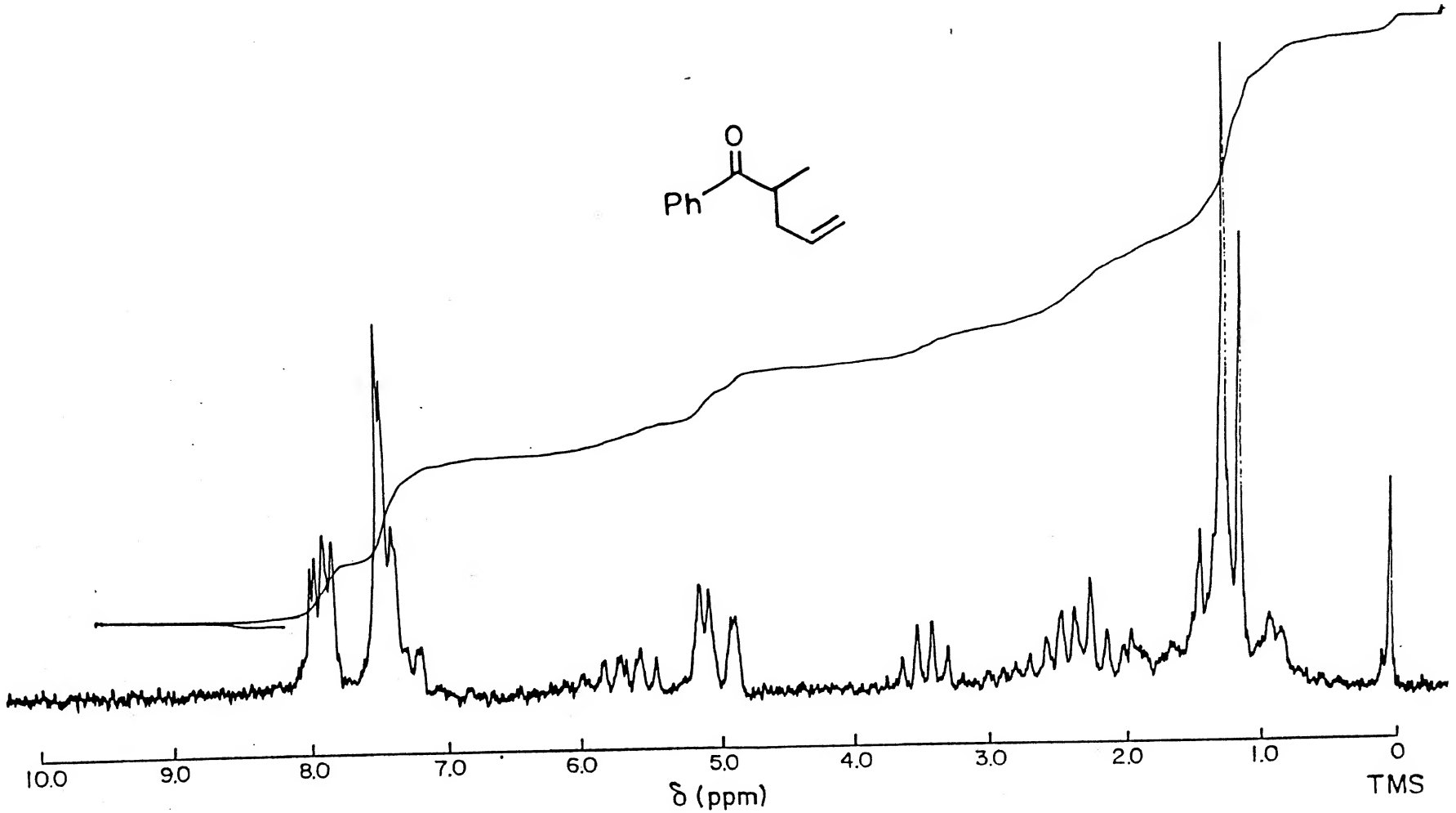
60 MHz ^{1}H NMR spectrum of the compound 55



60 MHz ^{1}H NMR spectrum of the compound 56



60 MHz ^{1}H NMR spectrum of the compound 57



60 MHz ^{1}H NMR spectrum of the compound G2

INTRODUCTION TO DEVELOPMENT OF NEWER SYNTHETIC METHODOLOGIES FOR ORGANIC SYNTHESIS

The development of new synthetic methods in organic synthesis is one of the areas of organic chemistry that has experienced a major renaissance during the past twenty years. Synthesis of a target molecule, whether it is a natural product or a deliberately chosen non-naturally occurring compound, involves a number of steps. Each step, in fact, represents a synthetic method involving the utility of a reagent and a reaction or a synthon. Development of these synthetic methods with an aim to improve the efficiency of the process and selectivity (chemo, regio, stereo- and enantioselectivities) is being addressed seriously by synthetic organic chemists. In this chapter we have reported four synthetic methods. The first three deal with the conversion of olefins into vicinally functionalised compounds and the fourth one is an improvisation of isomerisation of glycidic esters with a zeolite catalyst.

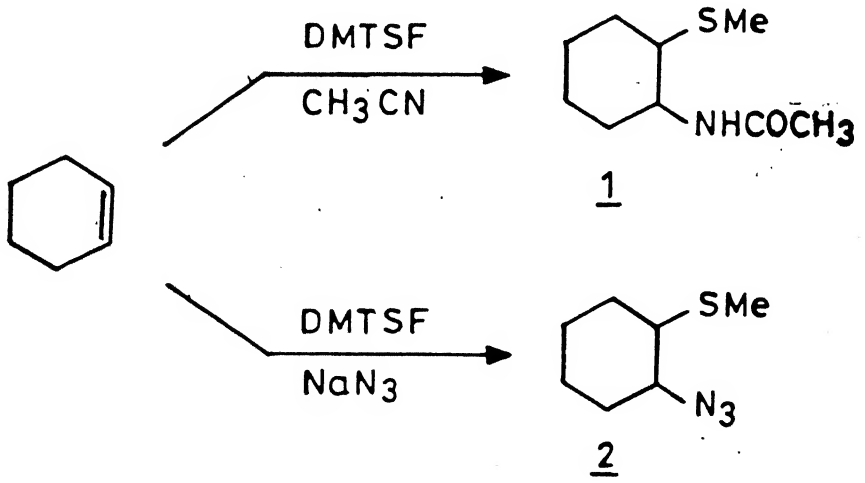
CHAPTER II

PART A

ONE POT SYNTHESIS OF NITROACETAMIDES FROM OLEFINS WITH CERIC AMMONIUM NITRATE-SODIUM NITRITE-ACETONITRILE REAGENT SYSTEM

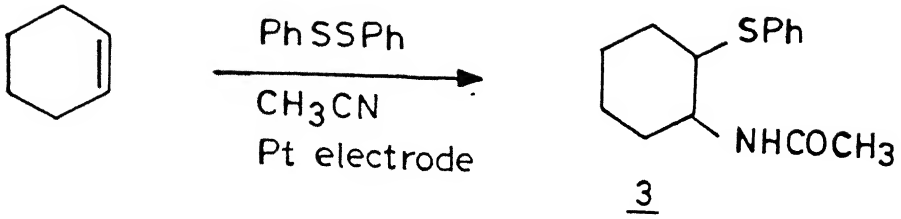
II.A.1 INTRODUCTION

The diversity of electrophilic addition to alkenes affording vicinally substituted products of synthetic importance was recently increased[1]. In particular, methods of addition of a nitrogen and of a second heteroatom substituent have been developed. By use of dimethyl (methylthio) sulphonium tetrafluoro borate as a sulphenylating agent and by appropriate choice of the nitrogen nucleophile, vicinal addition with the introduction of nitrogen at different oxidation levels can be achieved (Scheme 1). Thus, access to vicinally substituted amino sulphides from azido sulphides or nitrosulphides is readily possible.



SCHEME - 1

It has been reported that by the use of alternative sulphur electrophiles such as diphenyl disulphide[2] and arylsulphenyl[3] compounds, reactions in acetonitrile afford products of acetamido sulphenylation (Scheme 2).



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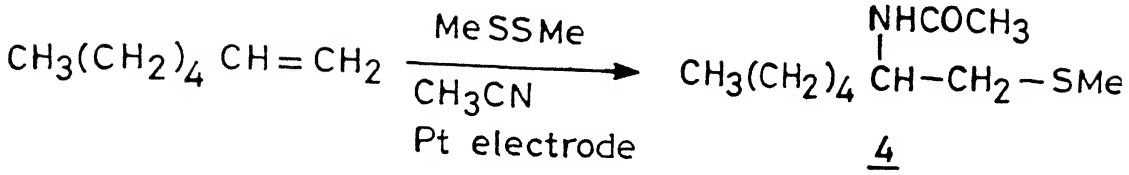
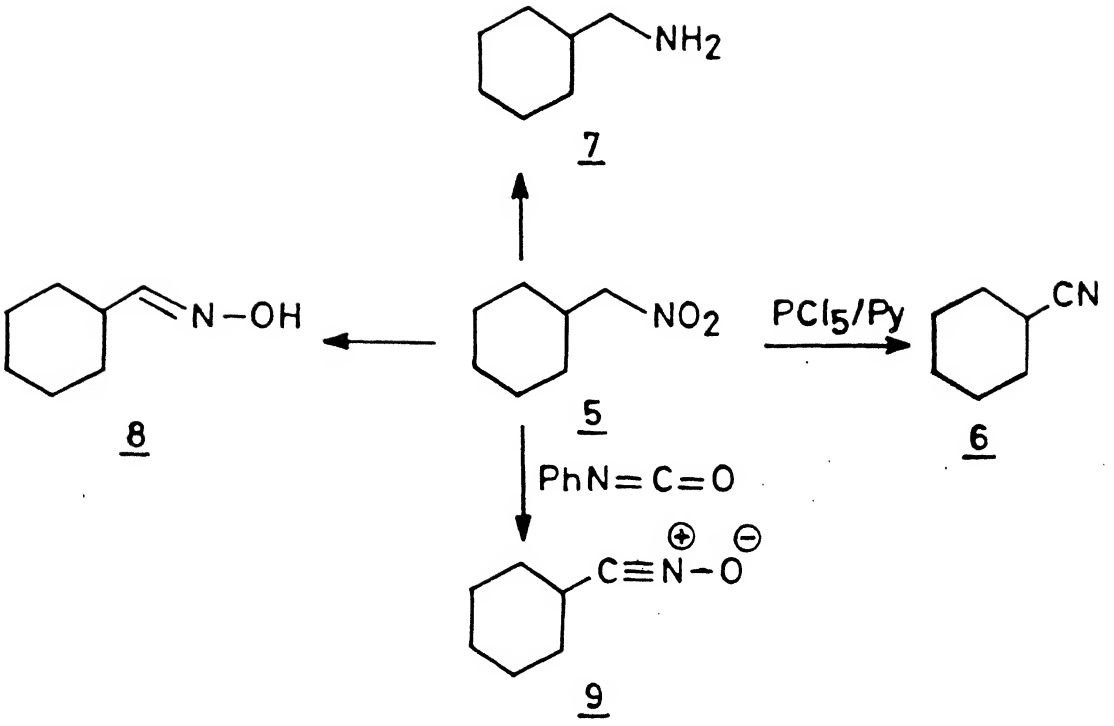


4

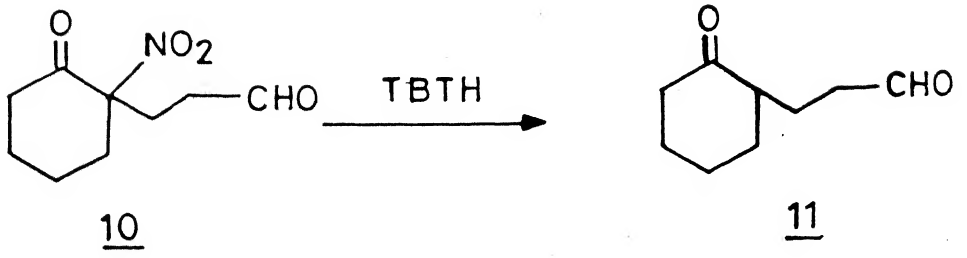
SCHEME-2

These acetamidation reactions occur as a result of the Ritter reaction on a subsequently generated carbocation after the initial attack of the electrophilic sulfur species on the olefins.

The chemistry of aliphatic nitro compounds has gained importance during the last one and half decades since the publication of an important review by Seebach[4]. The transformation of a primary and a secondary nitro group into another versatile functionality viz. a carbonyl group via the well known Nef reaction[5] has been well utilized in organic synthesis. In addition to this nitro compounds can also be easily transformed into other useful functionalities such as amines 7, oximes 8, nitrile oxides 9, etc. (Scheme 3). Deprotonation 'α' to the nitro group followed by C-C bond formation is also very useful in organic synthesis especially when reductive denitration with $n\text{-}Bu_3SnH$ is easily possible[7] (Scheme 4). On the other hand, tertiary nitro compounds undergo both inter as well as

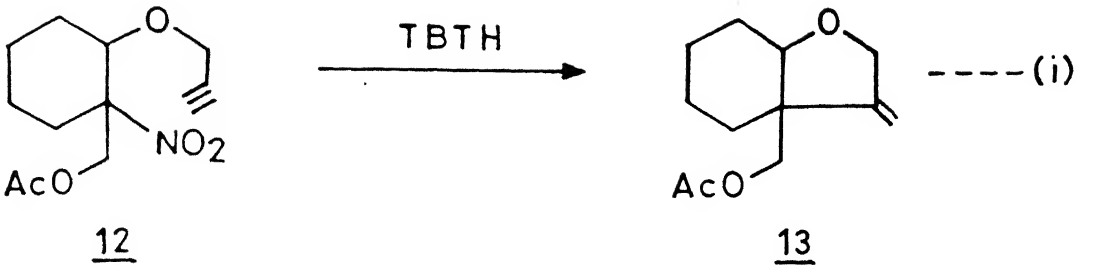


SCHEME - 3



SCHEME - 4

intramolecular C-C bond formations when treated with Bu_3SnH/AIBN via radical pathways[8]. These reactions have also found utility in carbohydrate chemistry[9] (Scheme 5).



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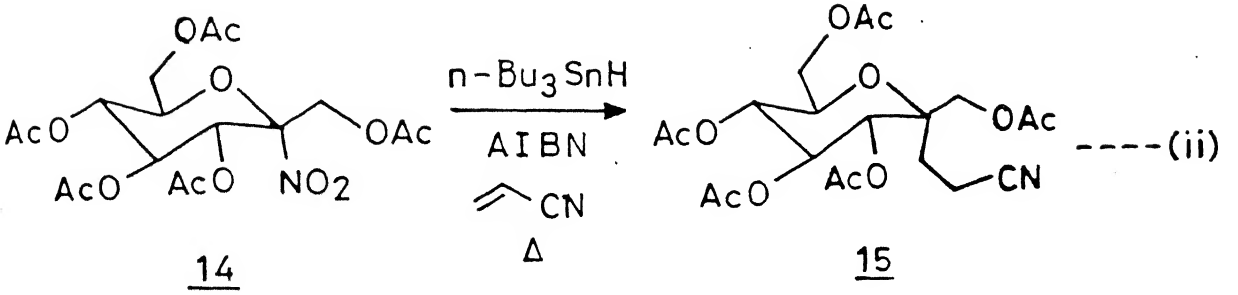

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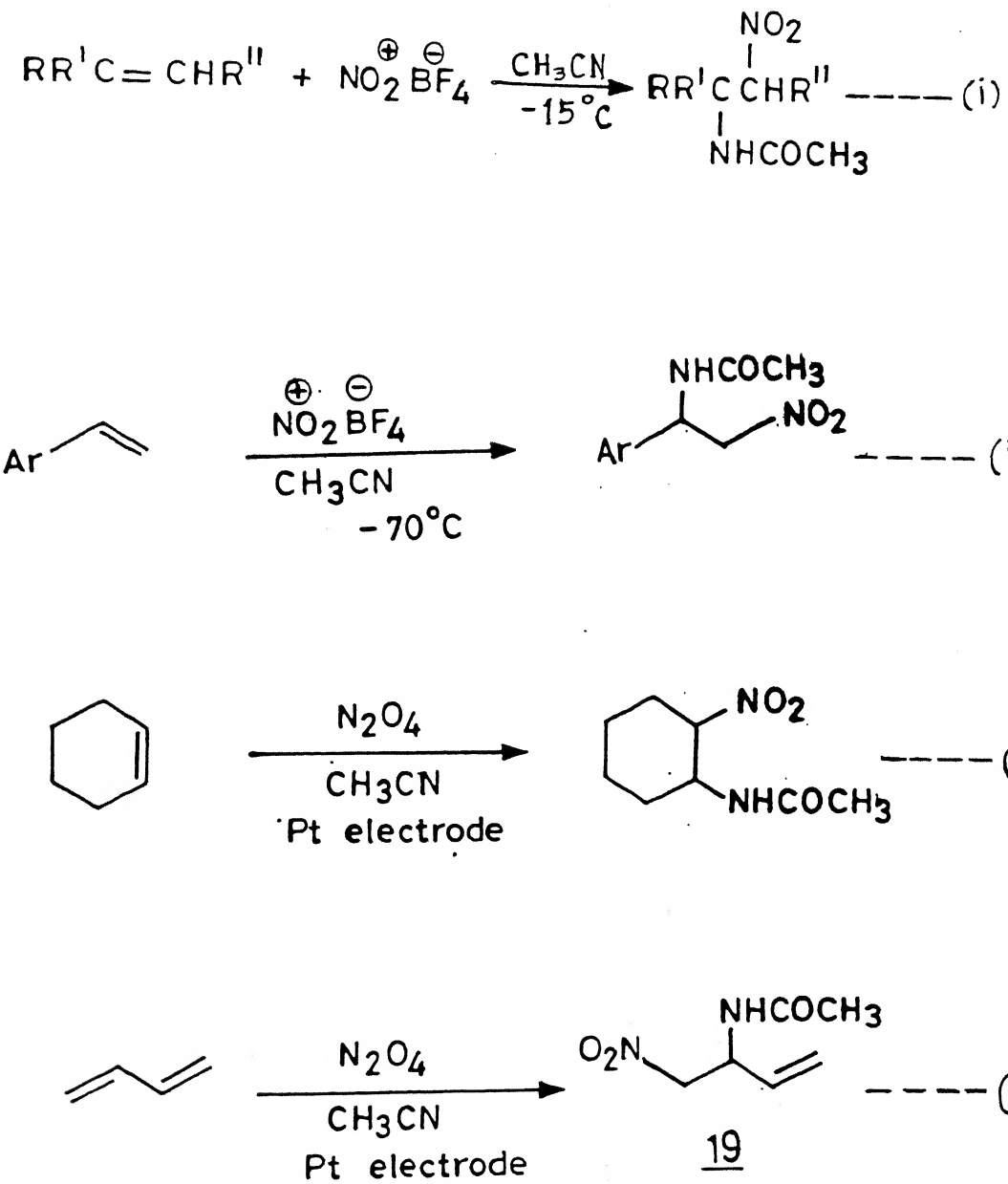
SCHEME-5

α-Nitro acetamides are prepared by treatment of olefins with $NO_2^+BF_4^-$ in acetonitrile solvent at -15°C[10] in a manner analogous to Ritter reaction (Eqn. (i), Scheme 6). Thus reaction of styrenes with $NO_2^+BF_4^-$ in acetonitrile affords good yields of products of nitroacetamidation[11] (Eqn. (ii), Scheme 6). In all the cases addition is highly regioselective to give Markownikoff products. Another procedure towards nitoracetamidation of olefins includes the use of electrochemistry in generating nitronium ion species. Oxidation of dinitrogen tetroxide at platinum electrode permits the generation of nitronium tetrafluoroborate in acetonitrile containing lithium tetrafluoroborate. Addition of olefin to this furnishes nitroacetamides in good yields[12] (Eqn. (iii), Scheme 6).

The same reaction has also been applied to prepare nitroamides from conjugated dienes[13]. Thus butadiene upon reaction under these conditions leads to the formation of compound 19 (Eqn. (iv), Scheme 6).

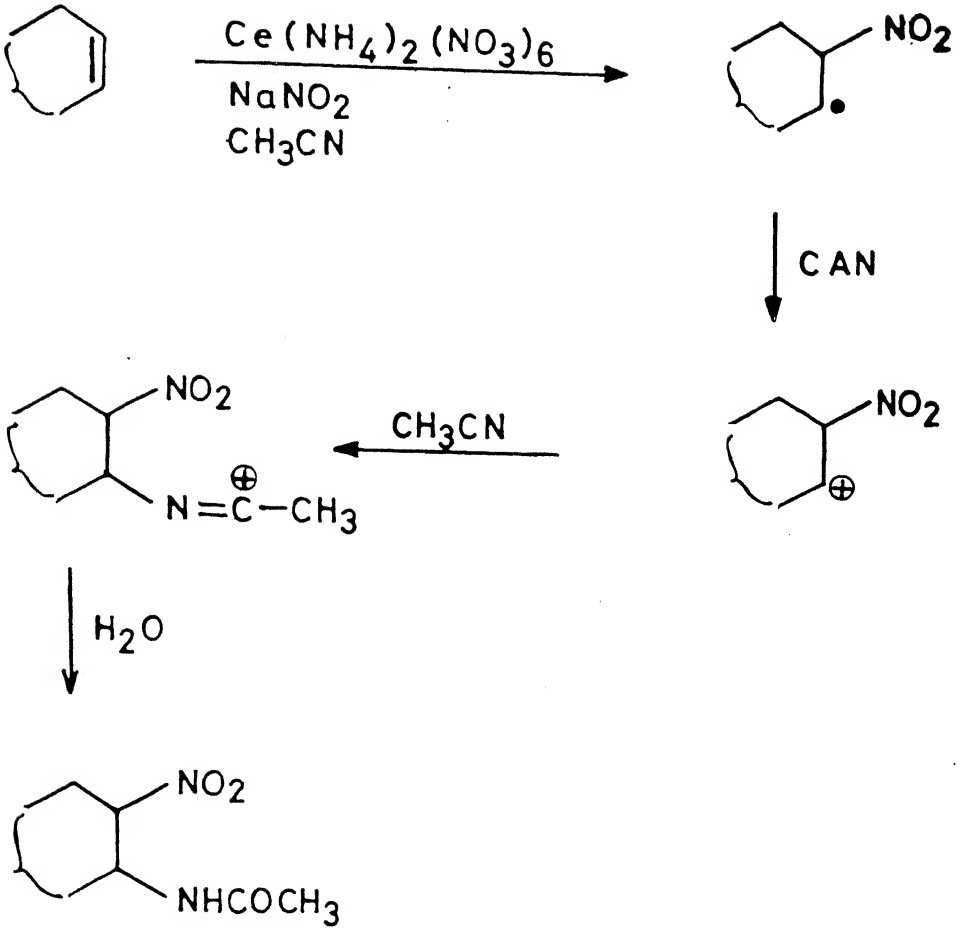


SCHEME-6

II.A.2 RESULTS AND DISCUSSION

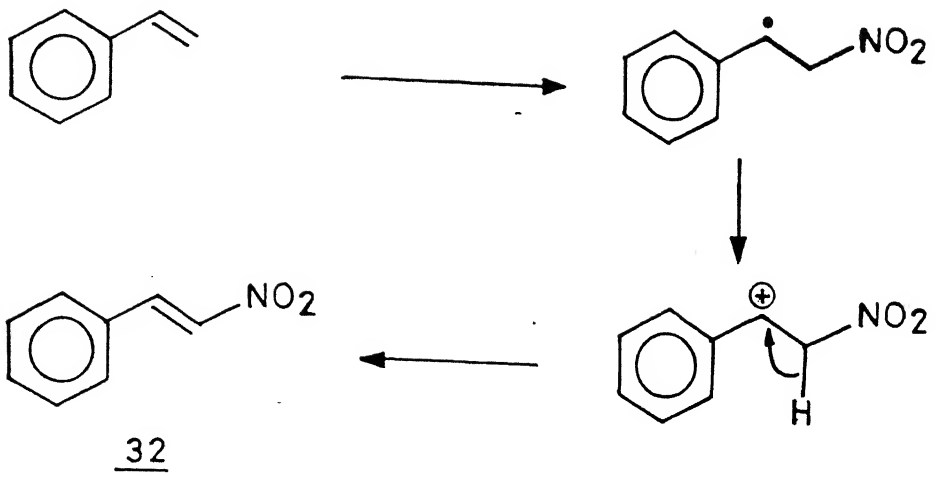
In the introduction part of this chapter a brief report from the literature is presented which highlights the importance of vicinally disposed nitroamides. It is apparent that the few methods which are reported in the literature towards the synthesis of nitroamides include either the use of a nitronium salt such as $NO_2^+BF_4^-$ or N_2O_4 in an electrochemical manner. Considering the importance of these vicinally disposed nitroamides, it appears that newer approaches towards them employing readily available and cheaper reagents and simple reaction conditions would be welcome.Our interest in the area of nitro chemistry has prompted us to find alternate sources of nitronium ions which could afford nitroamides from olefins. It is known in the literature that NaN_3 in the presence of ceric ammonium nitrate (CAN) forms $[N_3]^{\cdot}$ which readily adds on to an olefin. We, therefore, felt that $NaNO_2$ in an analogous manner could react with CAN to form $[NO_2]^{\cdot}$ which could then react with olefins. Indeed it was found that a variety of olefins gave the corresponding nitroacetamide upon treatment with $NaNO_2$ in the presence of CAN in acetonitrile.

We believe that species such as $[NO_2]^{\cdot}$ is generated by ceric ammonium nitrate under the reaction conditions which then adds on to the olefins to form carbon radicals. These radical intermediates are oxidised by another molecule of ceric ammonium nitrate into carbocations which are then trapped by acetonitrile to form nitroacetamides in a manner analogous to the Ritter reaction[14] (Scheme 7).



SCHEME-7

If the carbocation so formed loses a proton, instead of being trapped by acetonitrile, the corresponding nitroolefin is formed. This specially appears to be the case where the carbocation is well stabilised and the proton to be lost is very acidic (cf. Scheme 8).



32

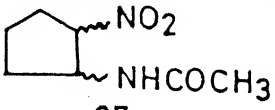
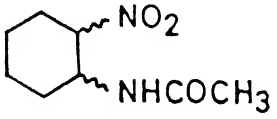
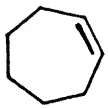
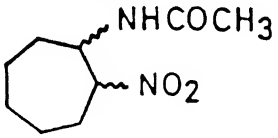
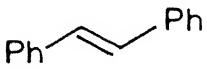
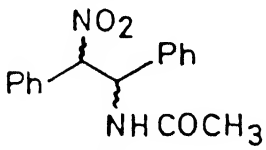
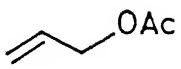
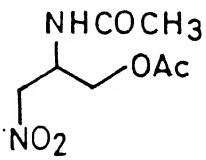
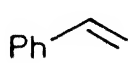
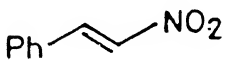
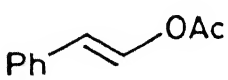
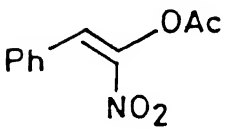
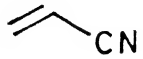
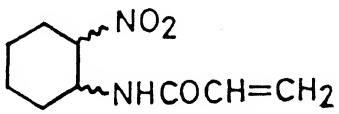
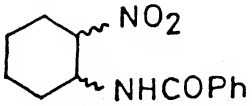
SCHEME-8

When cyclohexene 21 was treated with this reagent system, vicinal nitroacetamide 28 was formed in 58% yield. Its ^1H NMR spectrum showed peaks at δ 1.4-2.1 (11H, m, aliphatic with a singlet at 2.0 for -NHCOC<u>H</u>$_3$), 4.17-4.5 (1H, m, -CHNO$_2$), 5.5-5.7 (1H, m, -C<u>H</u>NHAc), 6.05-6.4 (1H, br s, -NH, exchangeable with D_2O). Its IR spectrum had peaks at 3300, 1640 and 1540 cm^{-1}. Mass spectrum had molecular ion peak at 186 corresponding to its molecular weight. Likewise cyclopentene and cycloheptene also gave the corresponding nitroacetamides 27 and 29 respectively and they were characterized fully by spectral means. Stilbene 23 gave nitroamide in moderate yield of 35%. Its ^1H NMR spectrum contained peaks at δ 1.9-2.1 (3H, s, -NHCOC<u>H</u>$_3$), 6.0-6.4 (2H, dd, -C<u>H</u>-NO$_2$, C<u>H</u>NHCOCH$_3$), 7.0-7.7 (10H, m, aromatic), 7.9-8.0 (1H, br s, -NH, exchangeable with D_2O). IR spectrum showed absorption at 3320, 1650, 1530 cm^{-1}.

Styrene 25 and cinnamyl acetate 26 furnished nitro olefins 32 and 33 in excellent yields, rather than the expected nitroacetamides. But this observation is not surprising because in these cases carbocations are well stabilised and the proton to be lost is very acidic. While our work was at the final stages, this combination of $NaNO_2$ and CAN was used by Hwu et al to convert olefins into corresponding nitro olefins in acetic acid at high temperatures in sealed tubes. Under these conditions ordinary olefins also give the nitroolefins. However, our condition does not require acidic medium and acetonitrile interrupts the carbocation. Allyl acetate 24 upon treatment with this reagent system gave the nitroacetamide 31 in 21% yield. The lack of stereochemical preference in these reactions or involvement of neighbouring group participation through an acetyl moiety (cf. entry 5, Table 1) strongly supports the intermediacy of a carbocation. Furthermore, instead of acetonitrile, when acrylonitrile or benzonitrile was used, the corresponding nitroamides 34 and 35 were formed (cf entries 8 and 9) thus confirming the generality of the reaction.

In conclusion, we believe that this one pot nitroacetamidation is a useful reaction since it introduces two important functional groups in one step using simple conditions and readily available reagents.

TABLE 1

S. No.	Olefin	Product	Time (hr)	Yield (%)
1	20	 27	24	64
2	21	 28	24	58
3	 22	 29	24	71
4	 23	 30	10	35
5	 24	 31	10	21
6	 25	 32	5	88
7	 26	 33	10	81
8	21 +  27	 34	24	68
9	21 + PhCN	 35	24	71

II.A.3 EXPERIMENTAL

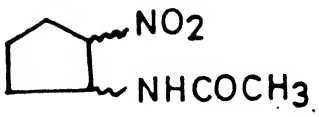
General

Ceric ammonium nitrate, sodium nitrite, acrylonitrile and benzonitrile were purchased from commercial sources and used as received.

General experimental procedure

To a stirred solution of an olefin (1 mmol) in 6 ml of acetonitrile was added sodium nitrite (10 mmol) and ceric ammonium nitrate (2 mmol). The reaction mixture was then stirred at room temperature for the time indicated in Table 1. It was then quenched with a saturated solution of sodium bicarbonate and extracted with ethyl acetate. The organic layer was washed with water and then with brine followed by drying over anhydrous Na_2SO_4. Removal of the solvent under reduced pressure yielded crude nitroacetamides. Purification by column chromatography yielded the pure product.

1-Acetamido-2-nitro cyclopentane 27

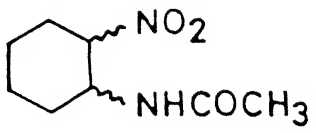


Yield : 64%

IR spectrum (neat) ν_{max} : 3300, 1630, 1500 cm^{-1}.

^1H NMR spectrum ($CDCl_3$) : δ 1.4-2.3 (9H, m, aliphatic with a singlet at 2.1 for $-NHCOC\underline{H}_3$), 4.7-5.0 (1H, m, $-\underline{C}HNO_2$), 5.5-6.0 (1H, m, $-C\underline{H}NHAc$), 6.17-6.4 (1H, br s, -NH, exchangeable with D_2O).

1-Acetamido-2-nitro cyclohexane 28



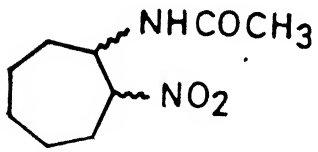
Yield : 58%.

IR spectrum (neat) ν_{max} : 3300, 1640, 1540 cm^{-1}.

^1H NMR ($CDCl_3$) : δ 1.4-2.1 (11H, m, aliphatic with a singlet at 2.0 for $-NHCOC\underline{H}_3$), 4.17-4.5 (1H, m, $-\overset{|}{C}HNO_2$), 5.5-5.7 (1H, m, $-\overset{|}{C}\underline{H}\overset{|}{N}HCOCH_3$), 6.05-6.4 (1H, br s, -NH, exchangeable with D_2O).

Mass spectrum m/z : 186 (M^+)

1-Acetamido-2-nitro cycloheptane 29



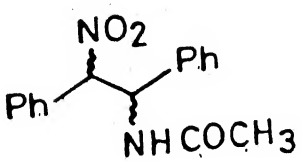
Yield : 71%

IR spectrum ($CDCl_3$) ν_{max} : 3300, 1640, 1540 cm^{-1}.

^1H NMR spectrum ($CDCl_3$) : δ 1.5-2.2 (13H, m, aliphatic with a singlet at 2.0 for $-NHCOC\underline{H}_3$), 4.17-4.5 (1H, m, $-CHNO_2$), 5.7-5.9 (1H, m, $-C\underline{H}NHCOCH_3$), 6.17-6.4 (1H, br s, -NH, exchangeable with D_2O).

Mass spectrum m/z :

1-Acetamido-1,2-diphenyl-2-nitro ethane 30



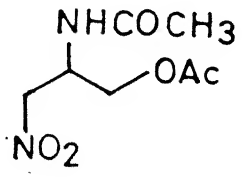
Yield : 35%

IR spectrum (neat) ν_{max} : 3320, 1650, 1530 cm^{-1}.

^1H NMR spectrum ($CDCl_3$) : δ 1.9-2.1 (3H, s, -NHCOC<u>H</u>$_3$), 6.0-6.4 (10H, s, aromatic), 7.9-8.0 (1H, br s, -NH, exchangeable with D_2O).

Mass spectrum m/z : 260 (M^+)

Allylacetate nitroamide <u>31</u>

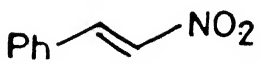


Yield : 21%

IR spectrum (neat) ν_{max} : 3400, 3200 (broad, NH), 1730, 1650, 1550 cm^{-1}.

^1H NMR spectrum ($CDCl_3$) : δ 1.9-2.17 (6H, 2s, -OC(=O)-C<u>H</u>$_3$, -NHCOC<u>H</u>$_3$), 4.17-4.4 (2H, d, C<u>H</u>$_2$-NO_2), 4.5-4.8 (3H, m, -C<u>H</u>$_2$OAc, -CH-N<u>H</u>COCH$_3$), 6.2-6.37 (1H, br s, NH, exchangeable with D_2O).

β-Nitro styrene <u>32</u>

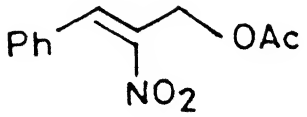


Yield : 88%

IR spectrum (CCl_4) ν_{max} : 1620, 1520 cm^{-1}.

^1H NMR spectrum (CCl_4) : δ 7.2-7.6 (5H, m, aromatic), 7.6 (1H, s, olefinic), 8.0 (1H, s, nitro olefinic).

β-Acetoxymethyl β-nitro styrene 33

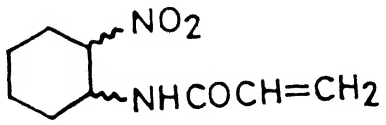


Yield : 81%

IR spectrum (neat) ν_{max} : 1740, 1640, 1530 cm^{-1}.

^1H NMR spectrum ($CDCl_3$) : δ 2.0 (3H, s, -OAc), 5.02 (2H, s, -$C\underline{H}_2$-OAc), 7.1-7.6 (5H, m, aromatic), 8.0(1H, s, olefinic).

1-Acrylamido-2-nitro cyclohexane 34

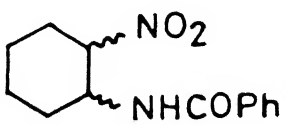


Yield : 71%

IR spectrum (neat) ν_{max} : 3300, 1640, 1540 cm^{-1}.

^1H NMR spectrum ($CDCl_3$) : δ 1.2-1.78 (8H, m, 4X-CH_2-), 4.8-5.0 (1H, m, $\diagdown\!\diagup CHNO_2$), 5.2-5.28 (1H, m, $\diagdown\!\diagup C\underline{H}$-NHCO-), 5.7-6.2 (3H, m, olefinic), 6.4-6.66 (1H, br s, $\diagdown\!\diagup NH$, exchangeable with D_2O).

1-Benzamido-2-nitro cyclohexane 35



Yield : 68%

IR spectrum (neat) ν_{max} : 3300, 1640, 1540 cm^{-1}.

^1H NMR spectrum ($CDCl_3$) : δ 1.1-1.8 (8H, m, 4X-CH_2-), 4.9-5.0 (1H, m, $\backslash CHNO_2$), 5.2-5.31 (1H, m, $\backslash \underline{CH}NHCOPh$), 6.6-6.8 (1H, br s, $\backslash NH$, exchangeable with D_2O), 7.1-7.8 (5H, m, aromatic).

II.A.4 REFERENCES

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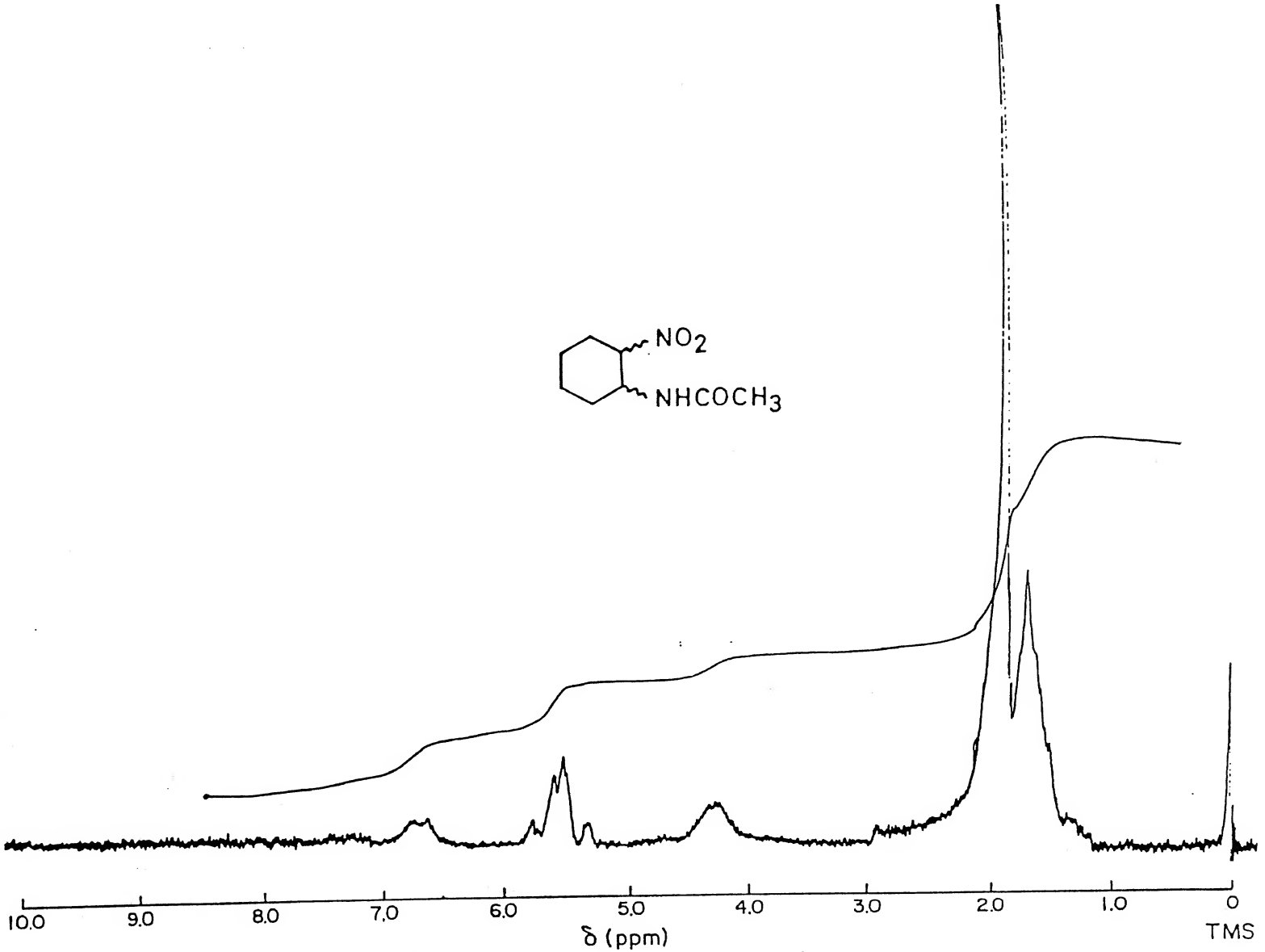


60 MHz ^{1}H NMR spectrum of the compound 28

CHAPTER II

PART B

ONE STEP SYNTHESIS OF α-NITROKETONES FROM OLEFINS WITH TRIMETHYLSILYLNITRATE-CHROMIUM TRIOXIDE REAGENT SYSTEM

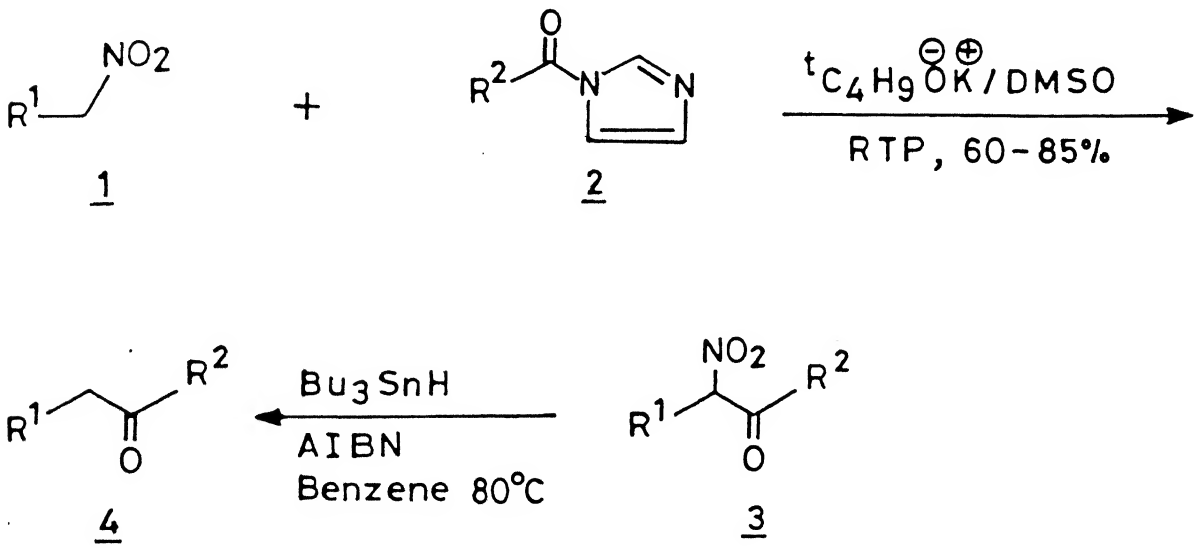
II.B.2 INTRODUCTION

Aliphatic nitro compounds have proven to be valuable intermediates, and the chemical literature continuously reports progress in their utilisation for the synthesis of a variety of target molecules. The vast preparative potential of aliphatic nitro compounds was extensively reviewed by Seebach et al[1] in 1979. Since then, several excellent reviews on the synthesis and reactions of nitroalkenes[2-5] and α-nitroketones[6-9] have appeared in the literature. Both α-nitroketones and conjugated nitroalkenes have been well utilised in organic synthesis. In this part, a brief introduction pertaining to the synthesis and reactions of α-nitroketones followed by the results of the present study is delineated.

Reactions of α-Nitroketones

α-Nitroketones are excellent synthons in organic synthesis. This mainly stems from the fact that the proton 'α' to the NO_2 group is fairly acidic, thus allowing its easy removal under mild conditions followed by C-C bond formation. Reductive denitration[10] with n-Bu_3SnH permits the synthesis of compounds without a NO_2 group. On the other hand, since the NO_2 group is capable of undergoing a variety of reactions it permits a number of functional group changes. These transformations include the well known Nef reaction[11], and reduction to the amino groups[12]. In the following few pages some selected literature data pertaining to the transformations using α-nitroketones has been delineated. This highlights the importance of these valuable synthons.

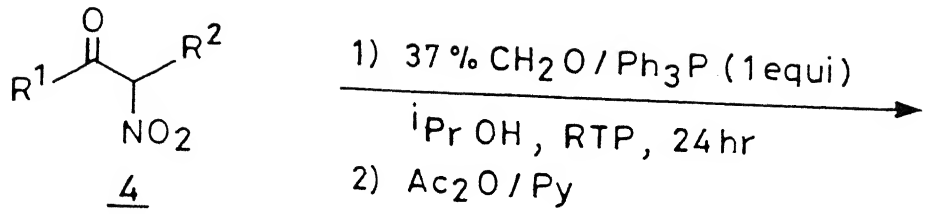
Ono et al[10] have developed a strategy for the preparation of ketones. Their procedure is based on the acylation of primary nitroalkanes using acylimidazoles and $^{\oplus}K\,^{t}BuO^{\ominus}$ as a base in DMSO followed by denitration of the resulting α-nitroketones with n-Bu_3SnH/AIBN. This procedure gives ketones in good to high yields (Scheme 1).



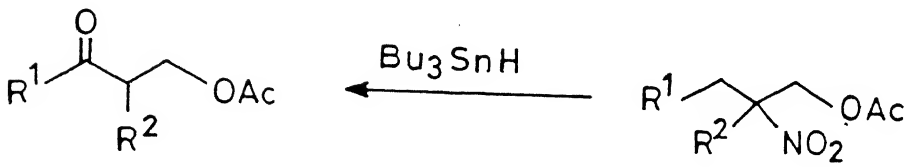
SCHEME -1

Ono et al[12] have also reported a new regioselective synthesis of α-methylene carbonyl compounds from α-nitroketones (or esters) via hydroxy or acetoxy methylated compounds (cf. Scheme 2).

α-Nitroketones and their high propensity to add on to α,β-unsaturated carbonyl compounds in Michael addition fashion are used in preparing 1,5-dicarbonyl compounds[13] (Scheme 3) which are, in turn, useful intermediates in organic synthesis.

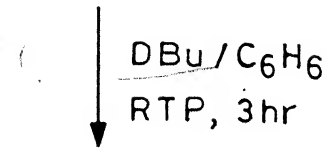

1) 37% CH_2O / Ph_3P (1 equi)
^iPr OH, RTP, 24 hr
2) Ac_2O / Py

4

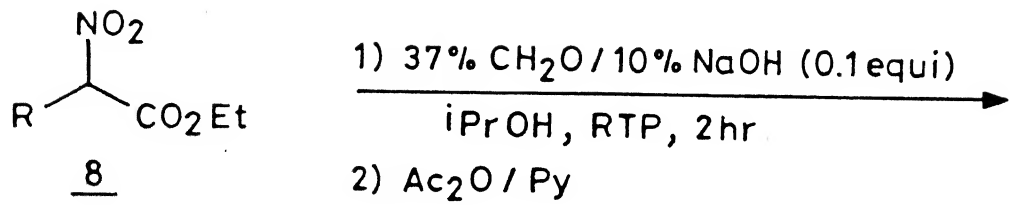

Bu_3SnH

6

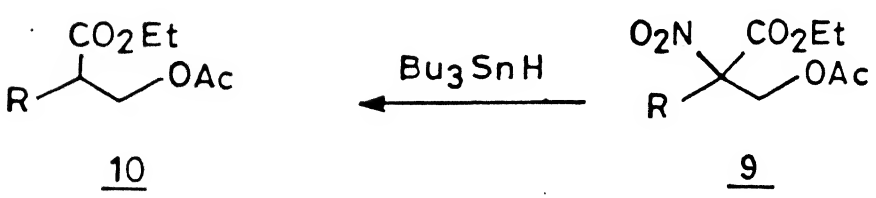
5


DBu / C_6H_6
RTP, 3 hr

7

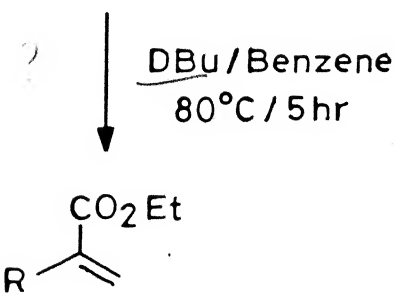

1) 37% CH_2O / 10% NaOH (0.1 equi)
iPrOH, RTP, 2 hr
2) Ac_2O / Py

8

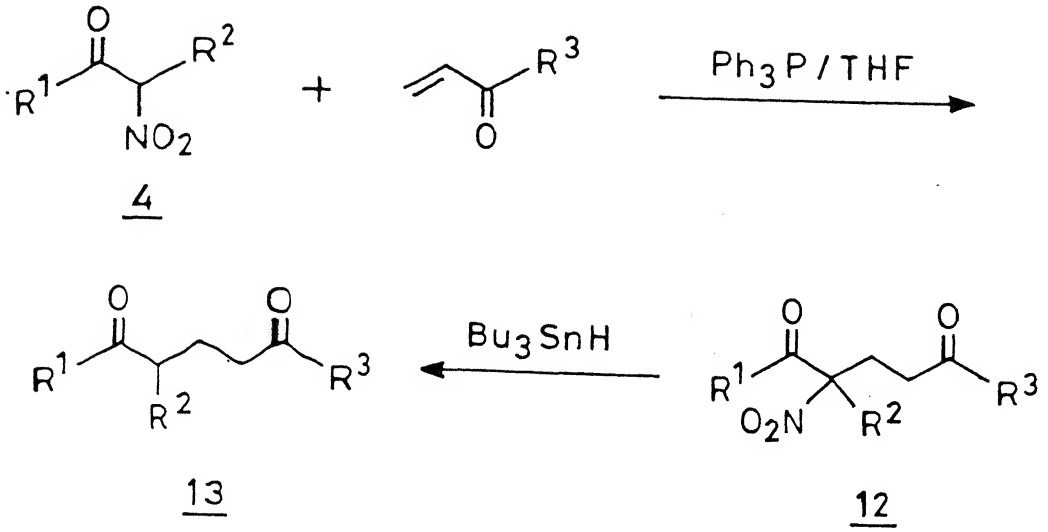

Bu_3SnH

10

9


DBu / Benzene
80°C / 5 hr

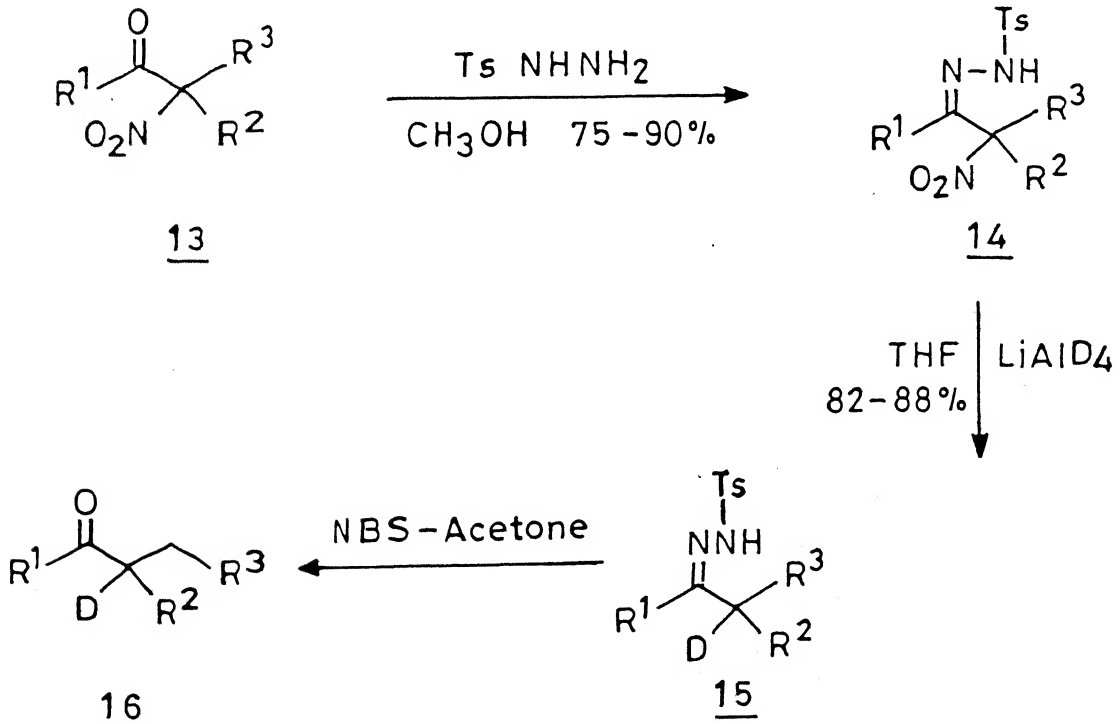
11



4 13 12

SCHEME-3

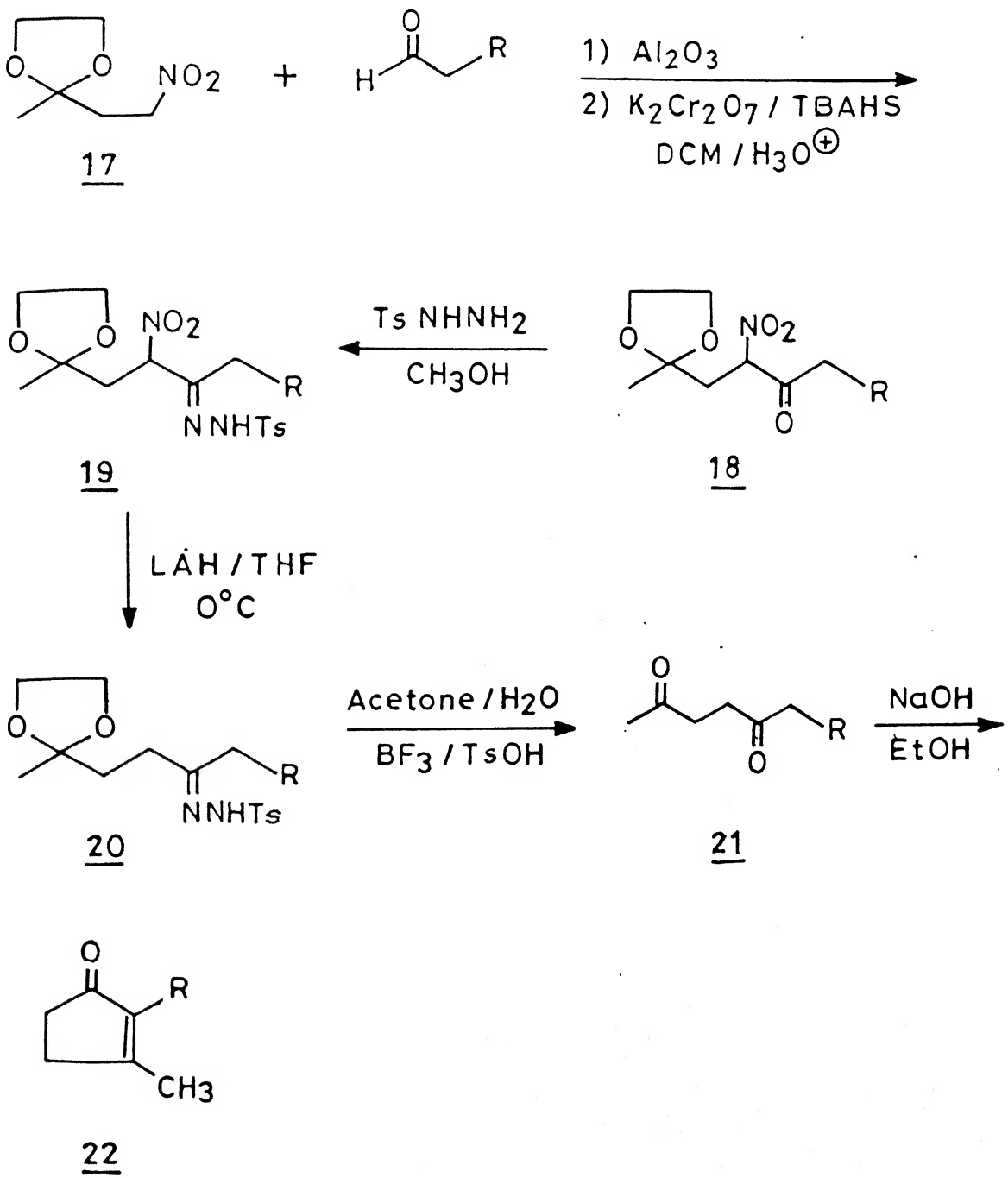
Synthesis of α-deuterated ketones from α-nitroketones has been reported by Rosini and Ballini[14]. Thus, tosylhydrazones of α-nitroketones are first denitrated with $LiAlD_4$. This allows the introduction of deuterium in place of nitro group. N-bromosuccinimide cleavage of tosylhydrazones then leads to the formation of α-deuterated ketones (Scheme 4).



13 14 15 16

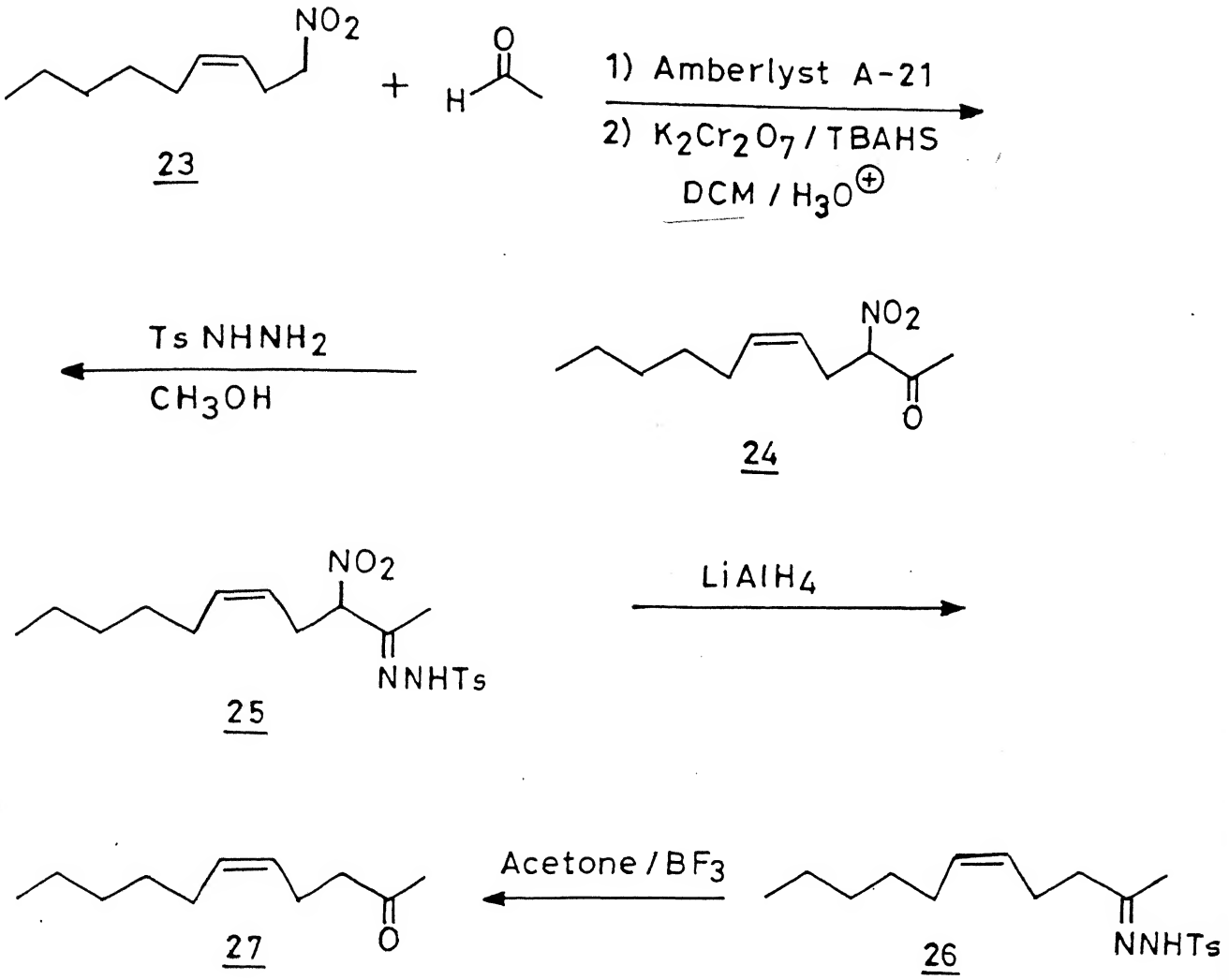
SCHEME-4

Importance of 1,4-dicarbonyl compounds in the synthesis of cyclopentanone moieties and subsequently derived natural products is well documented in the literature. Properly functionalised α-nitroketones (cf. compound 18, Scheme 5) have been synthesised using Henry reaction. These compounds have been transformed into 1,4-diketones[15] 21, through a series of reactions (cf. Scheme 5).



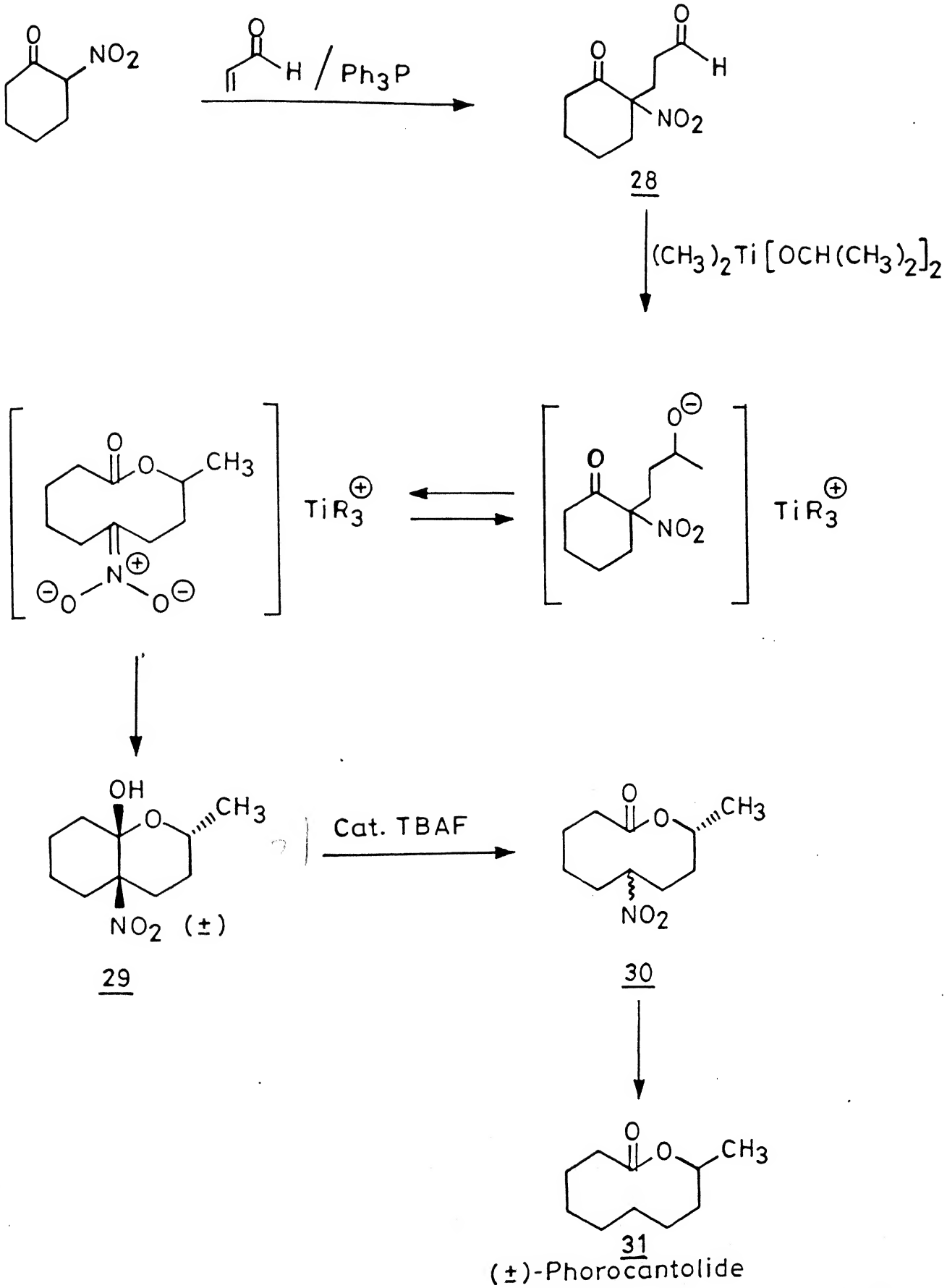
SCHEME - 5

A similar strategy has been applied to the synthesis of pheromone of Domolisus dorcasdorcas[16] (Scheme 6).

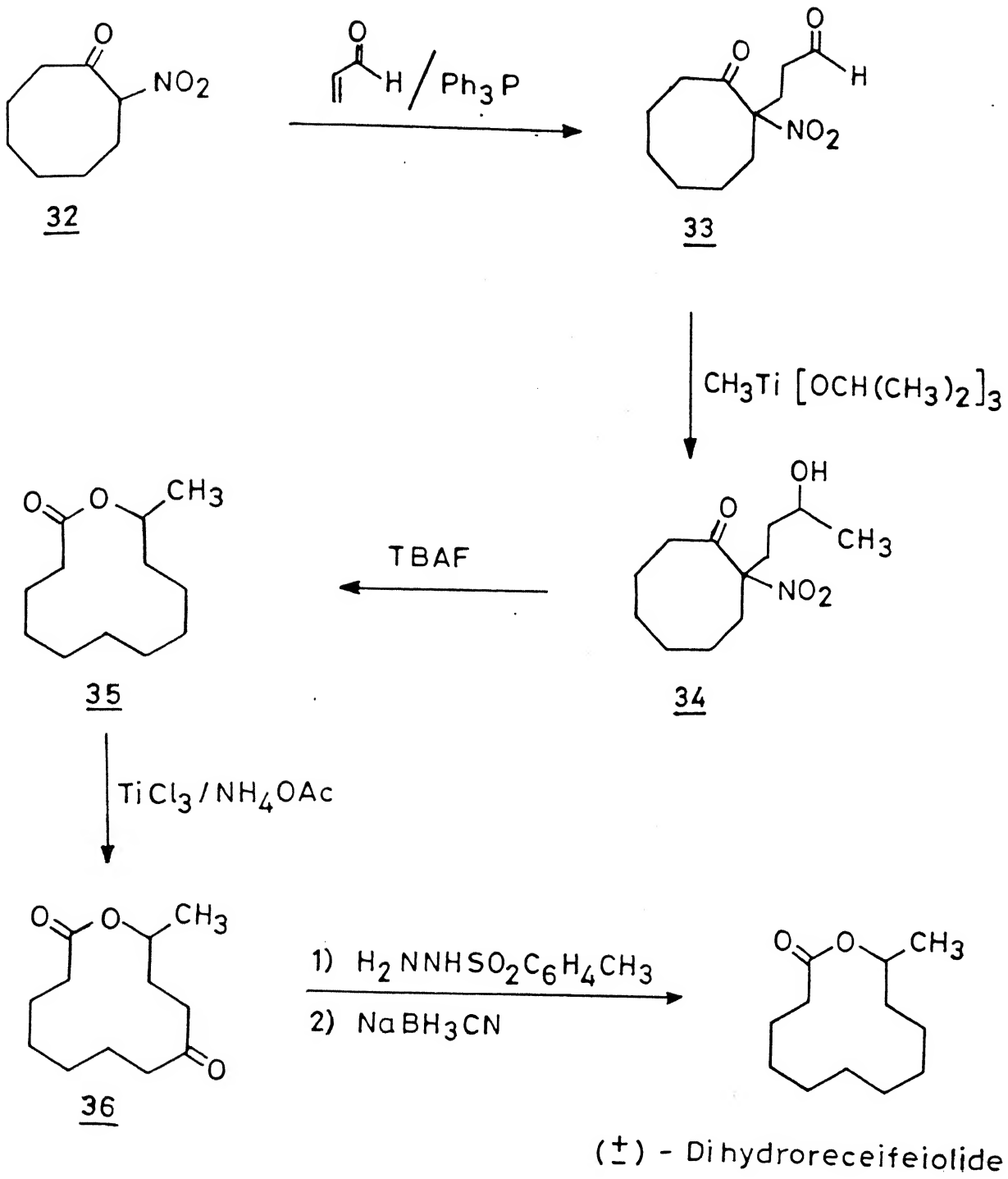


SCHEME - 6

A general procedure for the synthesis of macrocyclic lactones by ring enlargement reactions using α-nitroketones has been developed by Kostova and Hesse[17]. The Michael adducts of α-nitrocycloalkanones and acrylaldehyde are regiospecifically methylated with $CH_3Ti[OCH(CH_3)_2]_3$ or $(CH_3)_2Ti[OCH(CH_3)_2]_2$ at the aldehyde carbonyl group. Treatment of the so formed alcohols with

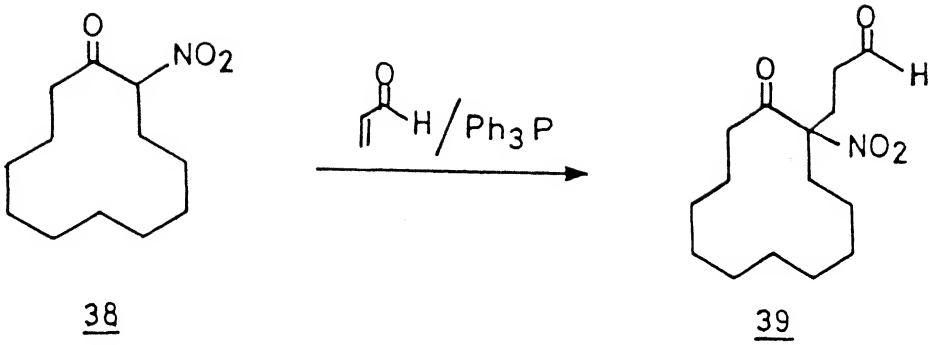

NO2
H / Ph3P
28
(CH3)2Ti[OCH(CH3)2]2
CH3
TiR3
OH
Cat. TBAF
29
30
31
(±)-Phorocantolide

SCHEME - 7

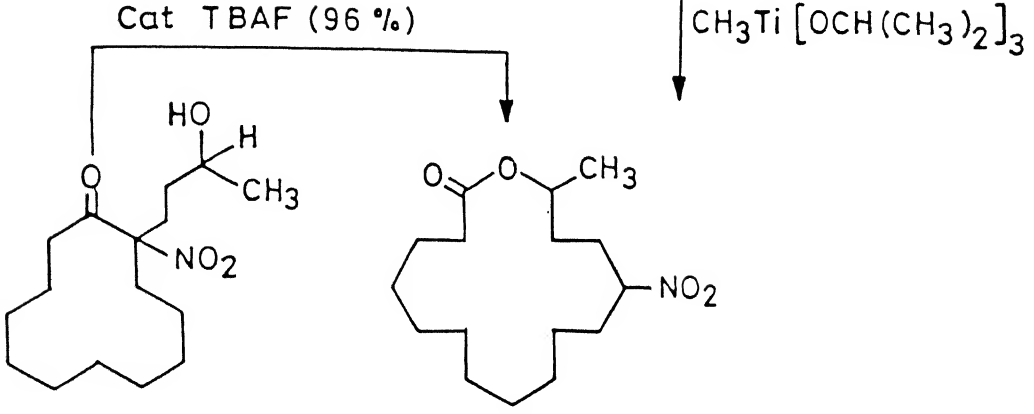


SCHEME 8

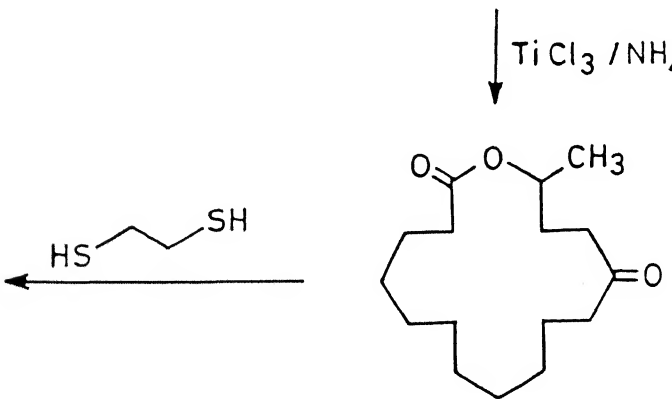
$Bu_4N^{\oplus}F^{\ominus}$ gives the lactones enlarged by four ring members. This method has been used to synthesise the 10-membered (±)-phoracantolide (Scheme 7), 12-membered (±)-dihydroreci-feiolide (Scheme 8) and (±)-15-hexadecanolide[17] (Scheme 9).



38 39



45.5 % 40 38 %



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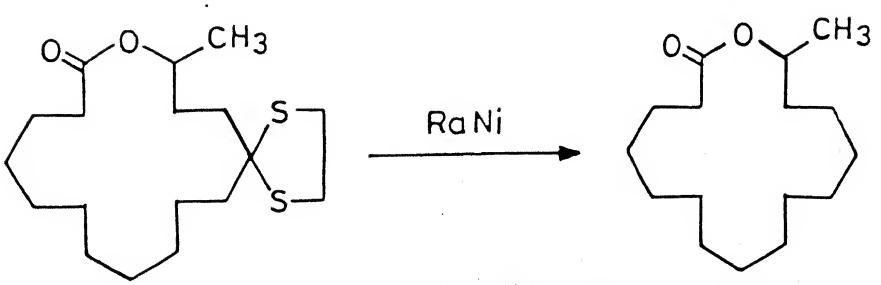
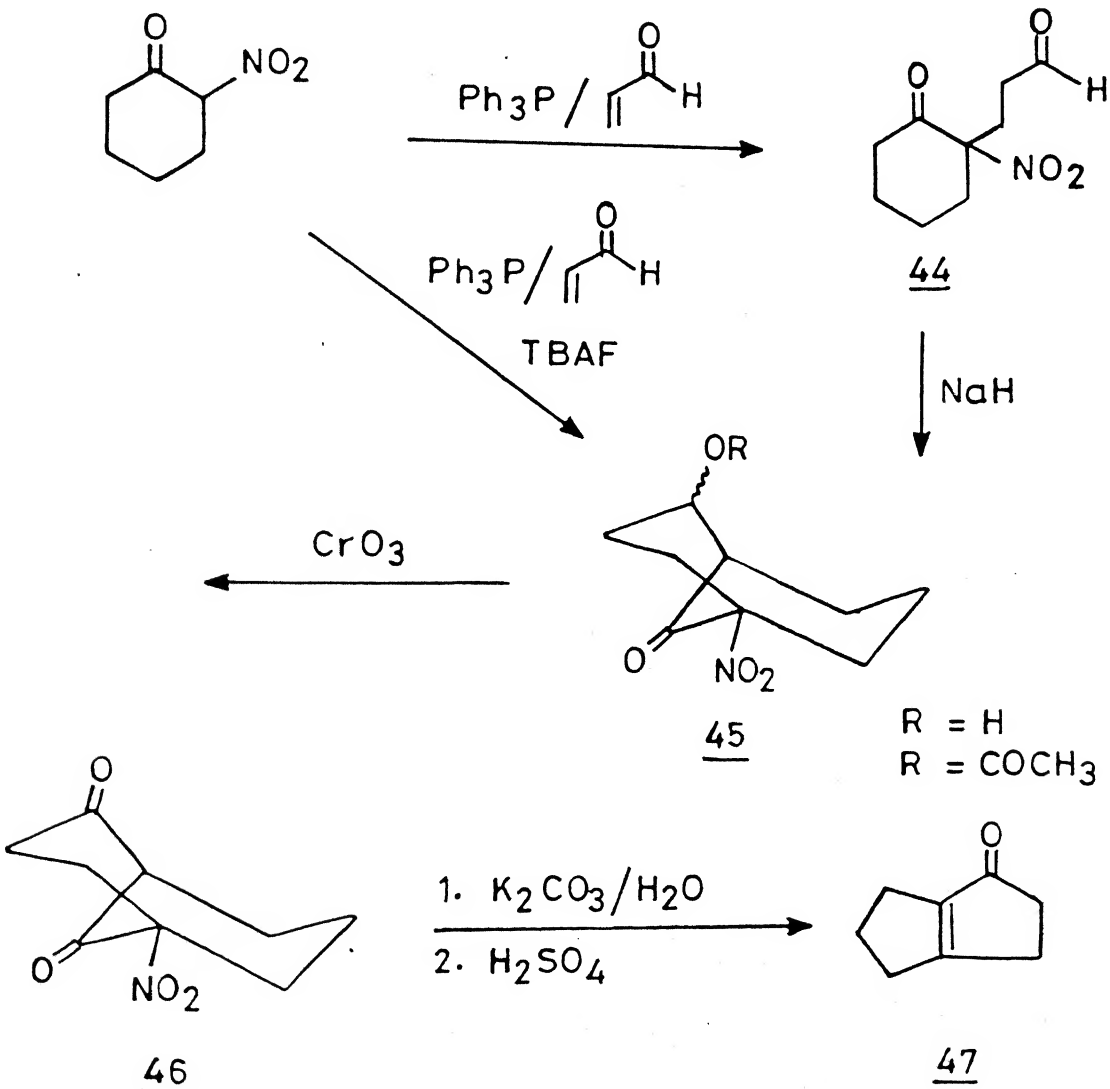


42 43

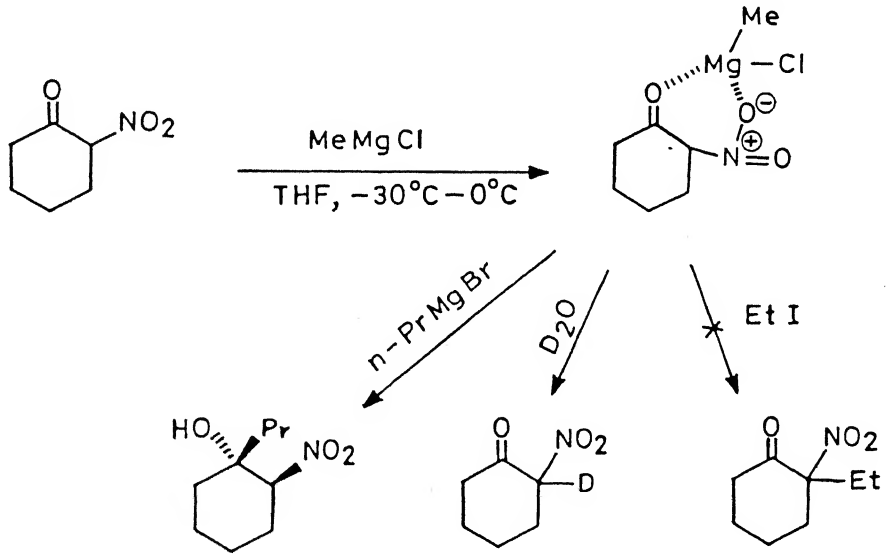
15-Hexadecanolide

Hesse and coworkers[18] have described an interesting approach towards the synthesis of bicyclo [3.3.0]oct-1(5)ene-2-one from α-nitro cyclohexanone. Thus, treatment of α-nitrocyclohexanone with acrylaldehyde in the presence of $Bu_4N^{\oplus}F^{\ominus}$ yielded the bicyclic product 45 , which was oxidised to the nitro diketone 46. The conversion of 45 to the title compound is achieved in nearly quantitative yield under unusual conditions, i.e., treatment with K_2CO_3/H_2O followed by H_2SO_4 [18] (Scheme 10).



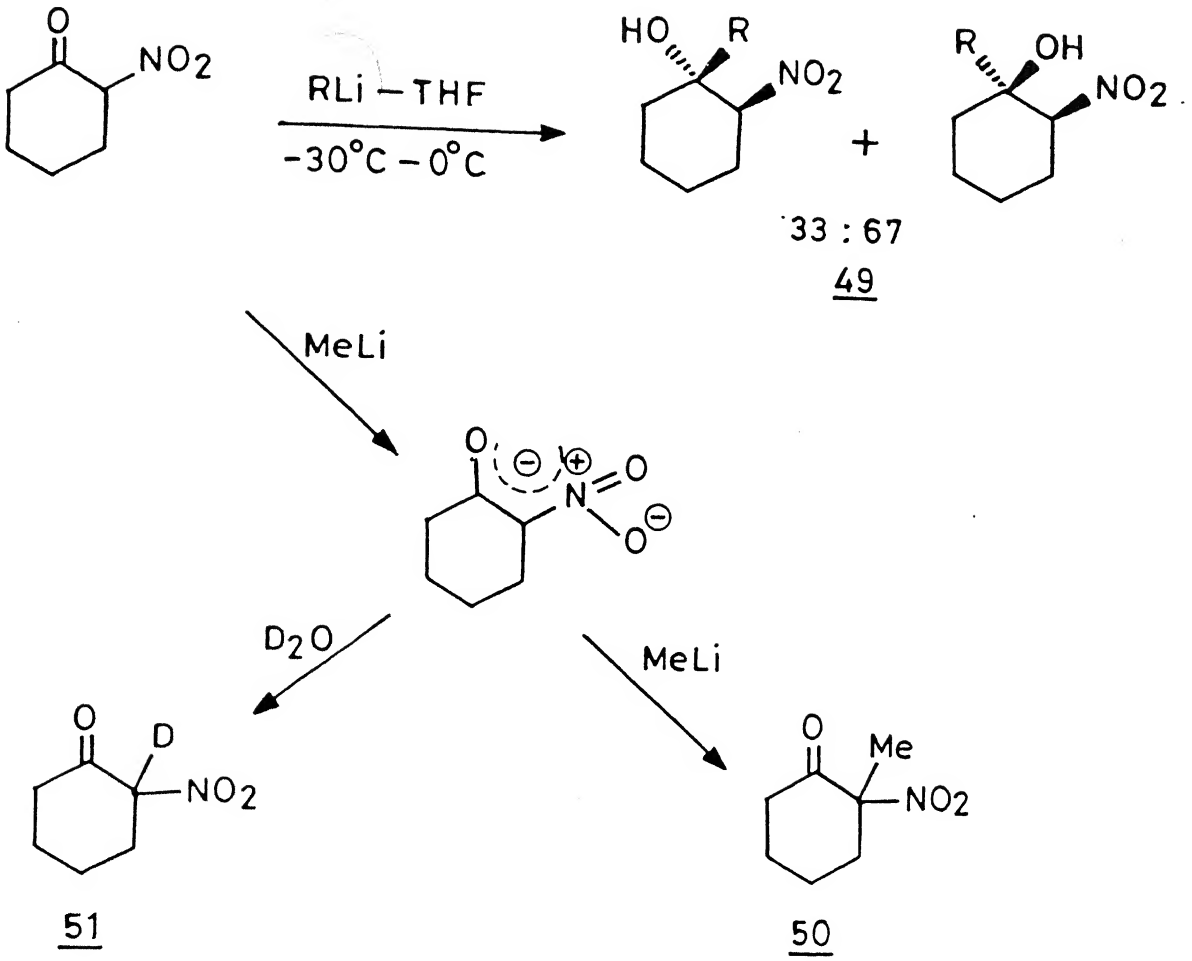
SCHEME -10

Reactivity of α-nitroketones towards organometallic reagents has been systematically studied by Ballini and coworkers[19] which has led to the efficient synthesis of tertiary β-nitroalkanols. Reaction of α-nitroketones with 2 equivalents of an organomagnesium or organolithium reagent led to these nitro alcohols. Unexpectedly, Grignard reagents did not deprotonate the 'α' acidic proton of α-nitroketones but instead strongly coordinated with the carbonyl and the nitro oxygens. A second equivalent of the reagent was thus necessary to carry out the addition. Magnesium reagents fail to react with open chain α-nitroketones because of rapid deprotonation and Grignard reagents are unable to attack the anion (Scheme 11).



SCHEME -11

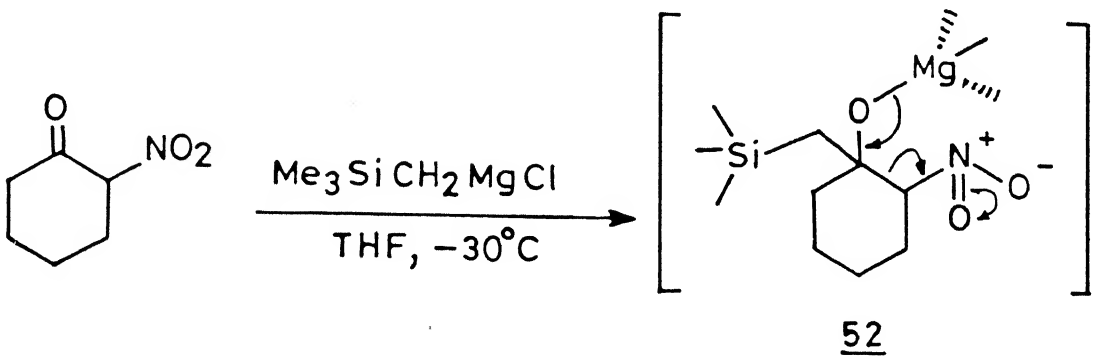
Organolithium reagents are stronger nucleophiles than organomagnesium reagents and can attack the deprotonated substrates. The diastereoselectivity of the reaction depends on the reagent used. Grignard reagents produced almost exclusively trans-nitroalkanols, whereas organolithiums show little or no selectivity with the same substrate (Scheme 12).



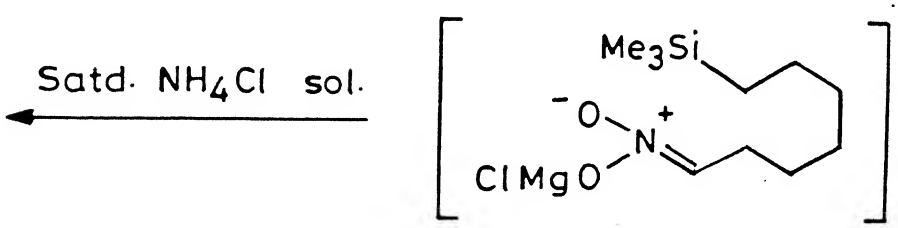
SCHEME-12

In pursuit of studying the reactivity of organometallic reagents, Ballini et al[20] have observed retro Claisen cleavage of α-nitrocycloalkanones using trimethylsilylmagnesium chloride. This has led to the synthesis of functionalised β-ketotrimethylsilanes (equation (i), Scheme 13). Treatment of α-nitrocycloalkanones with the Peterson reagent (Me_3SiCH_2MgCl) permitted the ring cleavage at -30°C. In this case also, 2 equivalents of the reagent were required. The unusual reactivity of these reagents has been explained by invoking the β-effect exerted by silicon. This high yielding process was, however, not feasible for large ring compounds.

The crucial role played by silicon atom was witnessed by a parallel experiment which was carried out using neopentylmagnesium bromide. In this case, reaction of the Grignard reagent with α-nitrocyclopentanone resulted in the formation of normal addition product only (equation (ii), Scheme 13).



52



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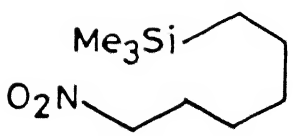
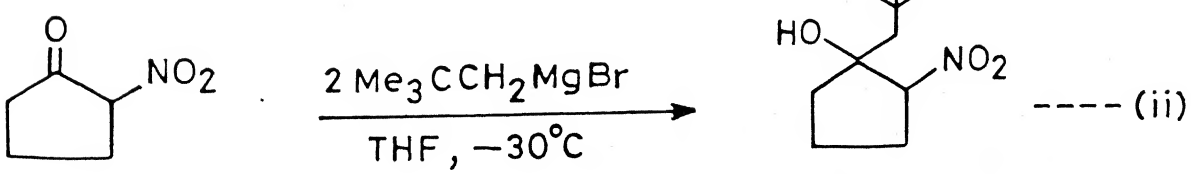


54

---- (i)

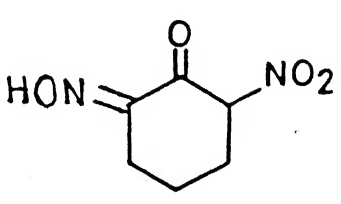


---- (ii)

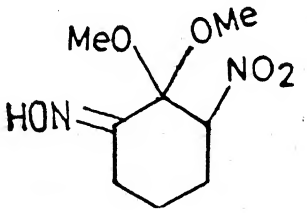
SCHEME - 13

In addition to the above described utility of α-nitroketones in organic synthesis, there are a few other reports which deal with the synthesis of some very useful compounds. Thus hexamethylenediamine (HMDA) is prepared by treating α-nitrocyclohexanone or its enolic isomer with H_2/NH_3 at 200-400°C in the presence of Ni-Co catalyst. In this manner 9% of HMDA and 16% of caprolactum are formed[21]. However, when a Re catalyst is employed, 47% of HMDA is formed[22]. ϵ-Caprolactum is prepared by the cleavage of α-nitrocyclohexanone with NH_3[23]. α-Nitrocyclohexanone is cleaved to give 6-nitro caproic acid (I) in the presence of 6-amino caproic acid (II). (I) is hydrogenated to give (II), which upon heating with water yields ϵ-caprolactum[24].

α-Nitrocyclohexanone is utilised in the synthesis of some fertilizers like (A). This is useful in the control of plant fungal diseases, especially coffee rust disease. It is prepared from α-nitrocyclohexanone by treatment with ≥ 10 wt % SO_2 at -30°C to 0°C with a nitrosating agent, and MeOH in the presence of HCl for 0.5-4 hr. Successive treatment of (A) with alkali and acid gives (B) which is also active against rust diseases and highly compatible with other fertilizers[25]. 1-Heptadecanoylpiperidine, which is prepared by reaction of $CH_3(CH_2)_{15}COCH_2NO_2$ with piperidine, is used as foam stabiliser, water proofing agent, rust inhibitor and fuel oil additive[26].



A



B

Preparation of α-Nitroketones

C-Acylation of primary nitroalkane salts to form α-nitroketones has been accomplished with the aid of acyl cyanides in 30-70 % yield. No α-nitroketones are obtained from salts of secondary nitroalkanes. The nitroalkanes have attracted considerable theoretical interest since their initial discovery because of the ambivalency of their corresponding anions which permits substitution reactions to occur either at oxygen of the nitro group or at the carbon attached to the nitro group. Aromatic acyl cyanides and aliphatic acyl cyanides are used to establish the generality of this reaction. Lithium salts of nitroalkanes are found to be better than sodium salts, both from the standpoints of ease of preparation of salts and of yields of α-nitroketones obtainable[27] (cf. Scheme 14).

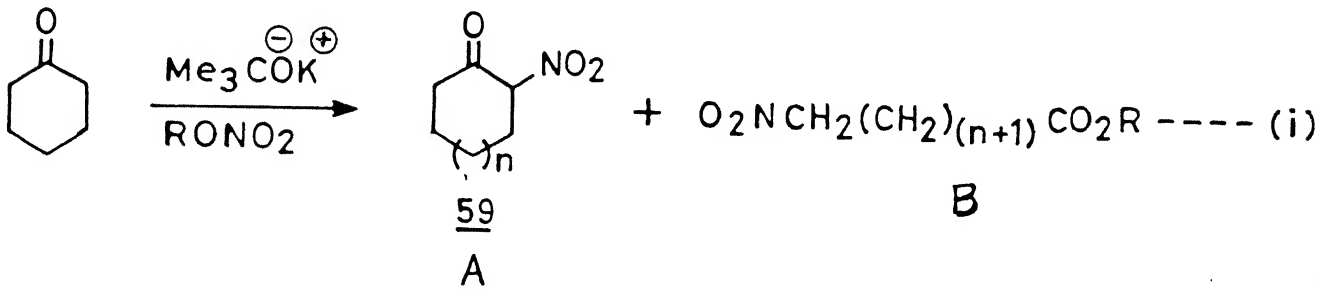
$$C_2H_4\overset{\ominus}{N}O_2\overset{\oplus}{Li} \;(\underline{56}) + C_6H_5COCN \xrightarrow[4\ hrs]{t\text{-}BuOH,\ 25^\circ C} C_6H_5COCH(NO_2)CH_3 \;(\underline{57},\ 50\%)$$

$$C_2H_4\overset{\ominus}{N}O_2\overset{\oplus}{Li} \;(\underline{56}) + CH_3COCN \xrightarrow{\quad\text{"}\quad} CH_3COCH(NO_2)CH_3 \;(\underline{58},\ 30\%)$$

SCHEME-14

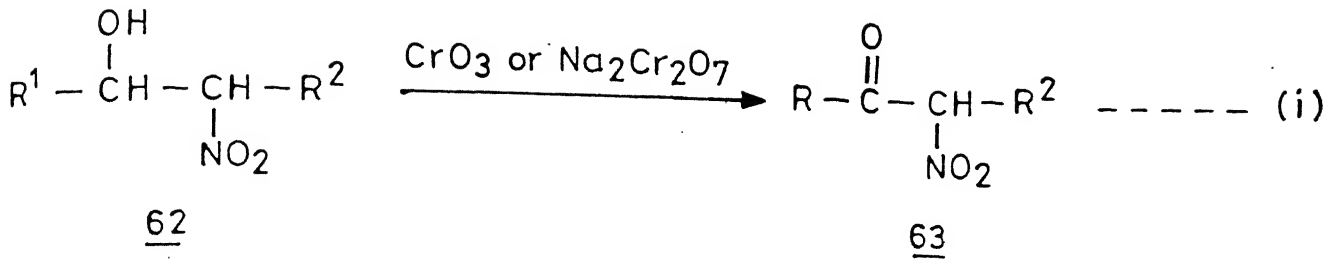
The mononitration of cycloalkanones with alkyl nitrates in the presence of potassium tertiary butoxide affords not only α-nitrocycloalkanones (A) but also ω-nitrocarboxylic esters (B). (equation (i), Scheme 15). The latter arises from a fragmentation

reaction which occurs during the nitration step and not during subsequent acidification, but cleavage is not caused by direct alkoxide attack except in the case where the resulting ketone is tertiary. The relative amounts of compounds A and B formed vary with ring size; the fragmentation being more pronounced in the middle ring region and with α,α'-disubstituted cycloalkanones. Fragmentation also takes place with aliphatic and arylalkyl-ketones[28]. High yields of α-nitroketones are obtained by the use of highly reactive acylimidazoles[29] as acylating agent on a dimethylsulfoxide solution of the lithium salt of nitroalkanones (equation (ii), Scheme 15).

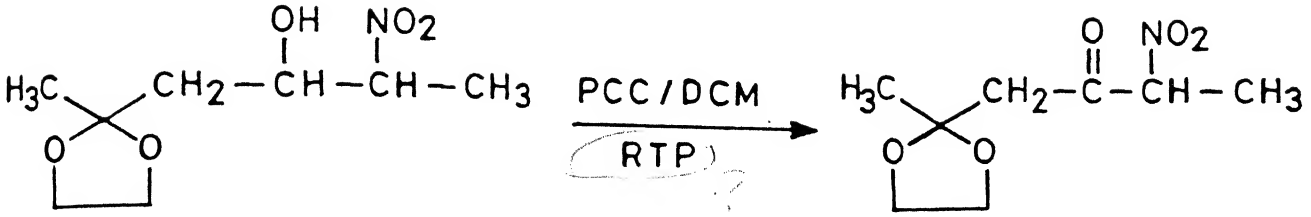


SCHEME-15

One of the classical ways of synthesising α-nitroketones[30-33] is the oxidation of α-nitroalcohols ~~which in turn are obtained by Henry reaction~~ (equation (i), Scheme 16). These oxidations are usually carried out by treating the alcohols with CrO_3 [30-31] or sodium dichromate[32] in strong acidic media (equation (ii), Scheme

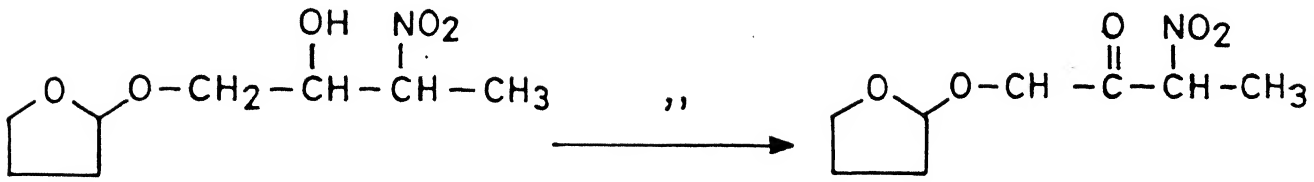


62 63 ------ (i)



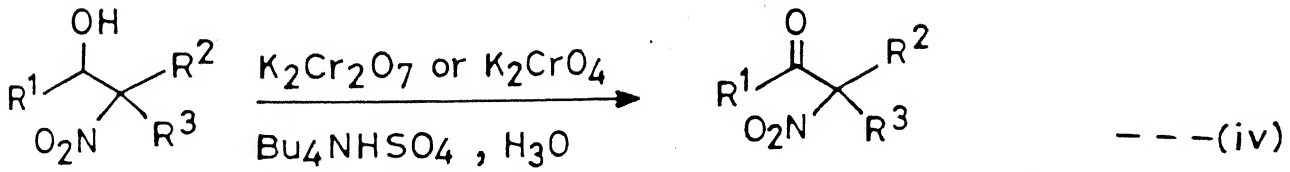
64 65 (78%)

--- (ii)



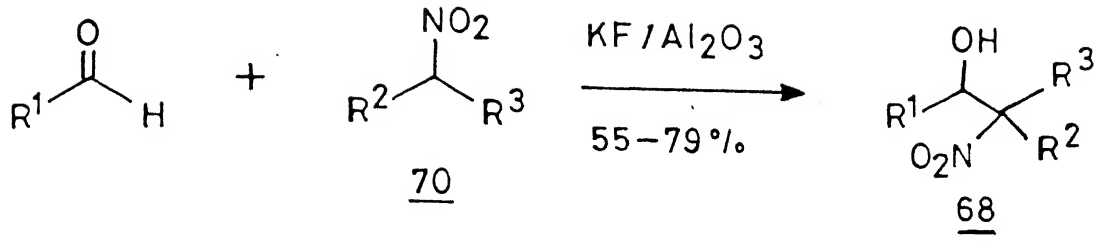
66 67

---(iii)



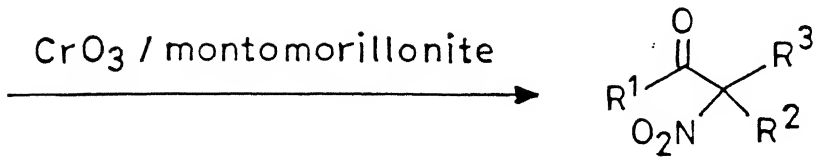
68 69 (80 – 90 %) ---(iv)

SCHEME-16



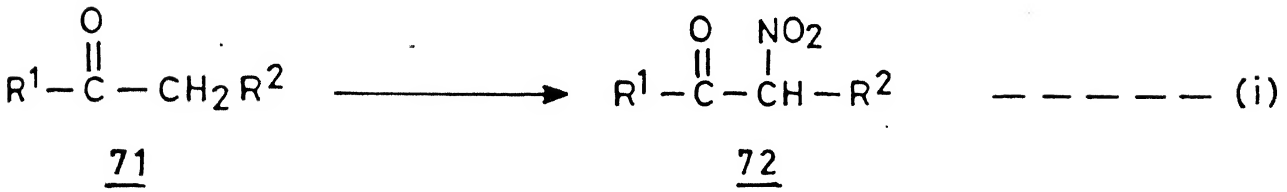
70

68

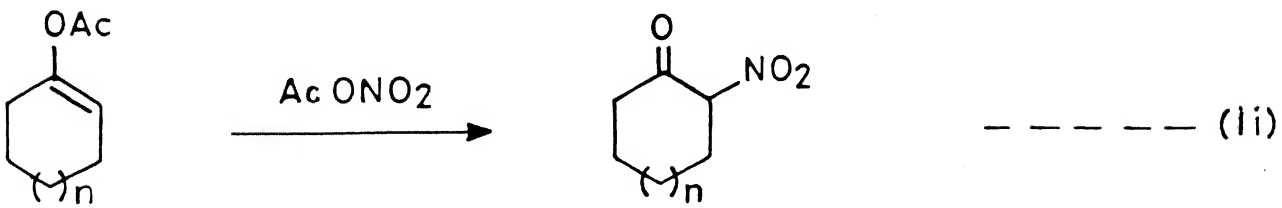


69

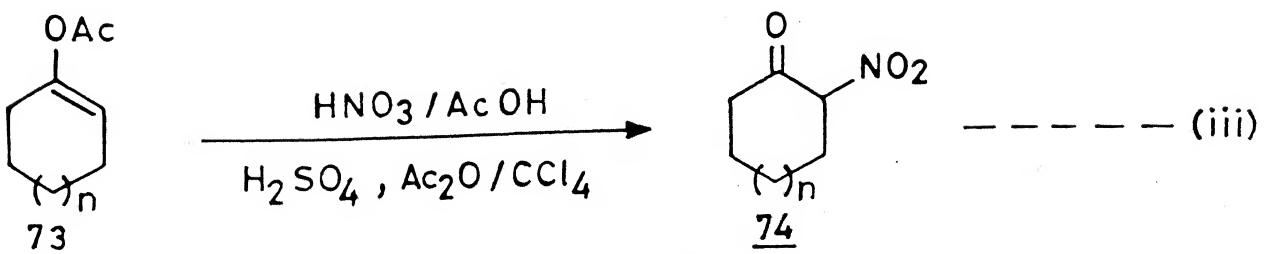
SCHEME-17



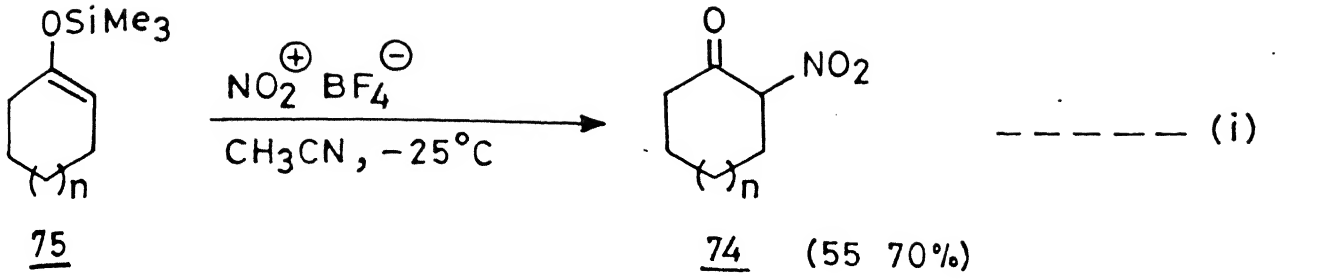
71 72 ------ (i)



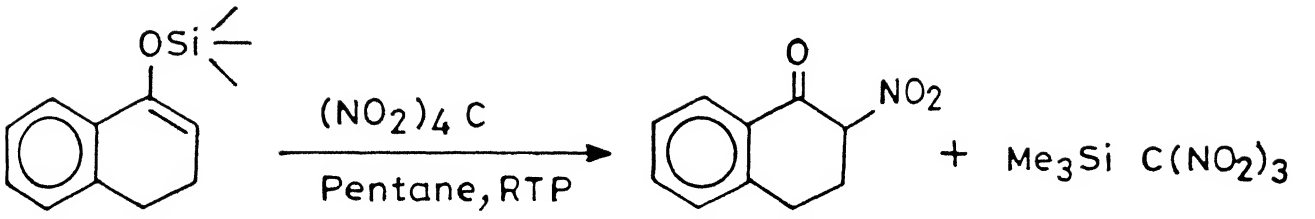
73 74 (51–88 %) ------ (ii)



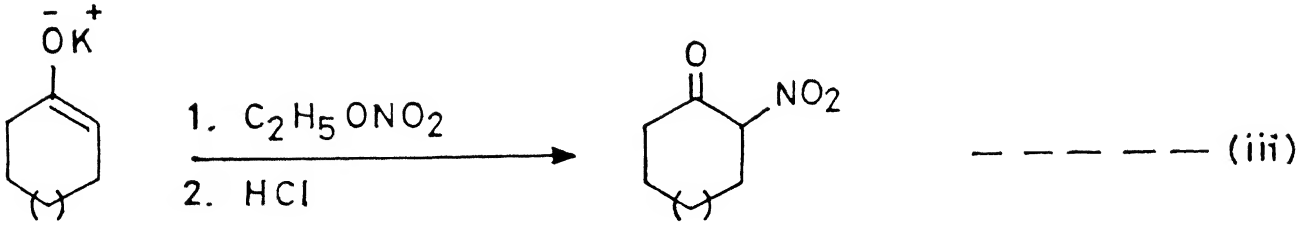
73 74 ------ (iii)



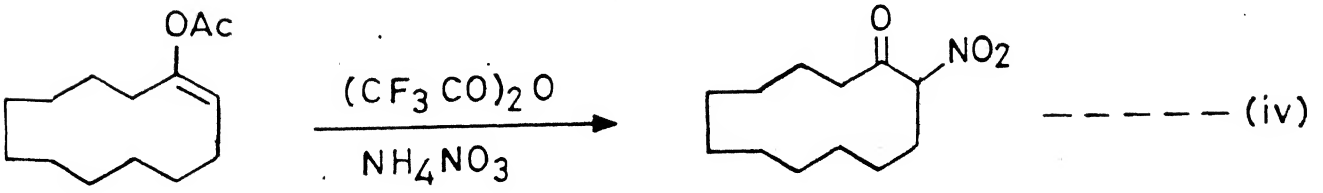
75 74 (55 70%) ------ (i)



76 77 (90 %) ----- (ii)



78 74 ------ (iii)



79 80 ----- (iv)

SCHEME -19

16). However, yields obtained are usually low.

But high yields could be obtained by the use of pyridinium chlorochromate[34] in dichloromethane at room temperature. Oxidation proceeds smoothly even with the substrates in which additional acid labile protecting groups are present. In fact, groups as THP ether or cyclic acetal survive chlorochromate oxidation (equations (iii) and (iv), Scheme 16).

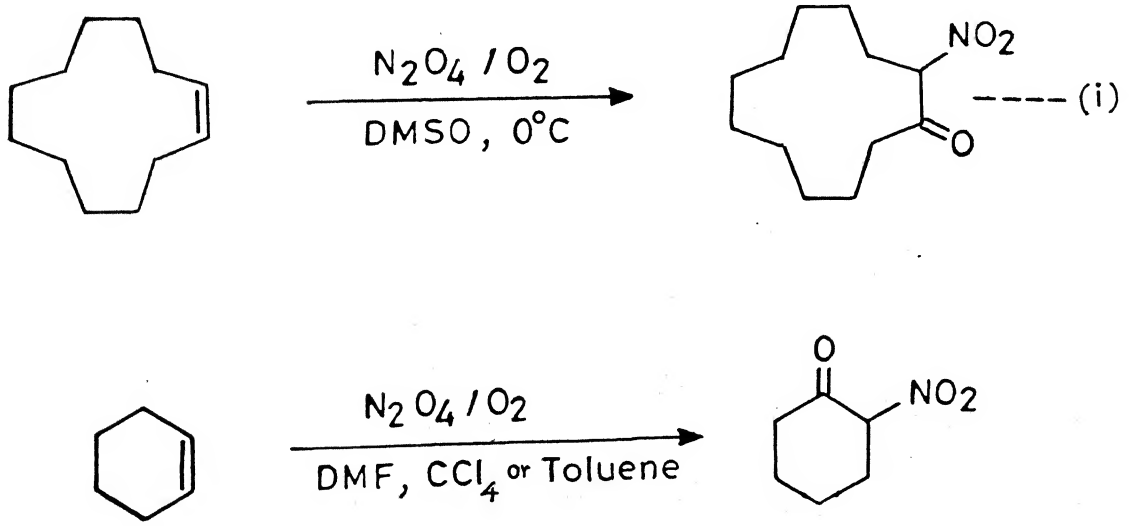
The only drawback of this procedure is that the reaction times are longer. However, this could be overcome by applying phase transfer techniques[35]. Reactions are carried out at -10°C to -5°C by slow addition of potassium dichoromate or potassium chormate and 30% H_2SO_4 to a solution of 2-nitroalkanols and tetra-n-butylammoniumhydrogensulphate (0.1 mole/mole) in dichloromethane. Reactions proceed smoothly to completion within 2 hours (equation (v), Scheme 16).

A modification of the Henry reaction and subsequent oxidation has been reported[36]. Thus, preparation of 2-nitroalkanols has been achieved by condensation of aldehydes with nitroalkanes in the presence of alumina supported KF and 2-nitroketones are produced by oxidation of nitroalkanols with montomorillonite supported CrO_3 (Scheme 17).

Another route of synthesising α-nitroketones is via electrophilic nitration of ketones with HNO_3 (< 1% H_2O) in CCl_4 at 10°C [36] (equation (i), Scheme 18). Also, reaction of acetyl nitrate with enol acetates produces high yields of α-nitroketones[37] (equation (ii), Scheme 18). High purity α-nitroketones are also obtained by treating enol acetates in CCl_4

at $0^{o}C$ with catalytic amount of H_2SO_4 and equimolar mixture of AcOH and HNO_3 in Ac_2O (equation (iii), Scheme 18). α-Nitroketones are also obtained from enol silyl ethers by reacting with $NO_2^+BF_4^-$ [38] or $C(NO_2)_4$ [39] (Scheme 19). Enolates and enol ethers are also converted into the corresponding α-nitroketones[40]. This method is very well suitable for preparing α-nitrocyclopentanones, which are known to undergo facile ring cleavage. One more powerful source of nitronium ion is a combination of NH_4NO_3 and $(CF_3CO)_2O$ in $CHCl_3$, which has been used to nitrate enol acetates under mild conditions[41].

Apart from the above mentioned routes to α-nitroketones, one direct route to them is from olefins. This conversion is achieved by the use of N_2O_4 and an oxidising agent. Olefins are treated with N_2O_4 and O_2 in n-pentane or ether followed by DMSO. The yields are usually good[42] (equation (i), Scheme 20). An improved procedure includes reaction of olefins with N_2O_4-O_2 in toluene or CCl_4 in the presence of DMF or DMSO[43] whereby α-nitroketones of very high purity are obtained.



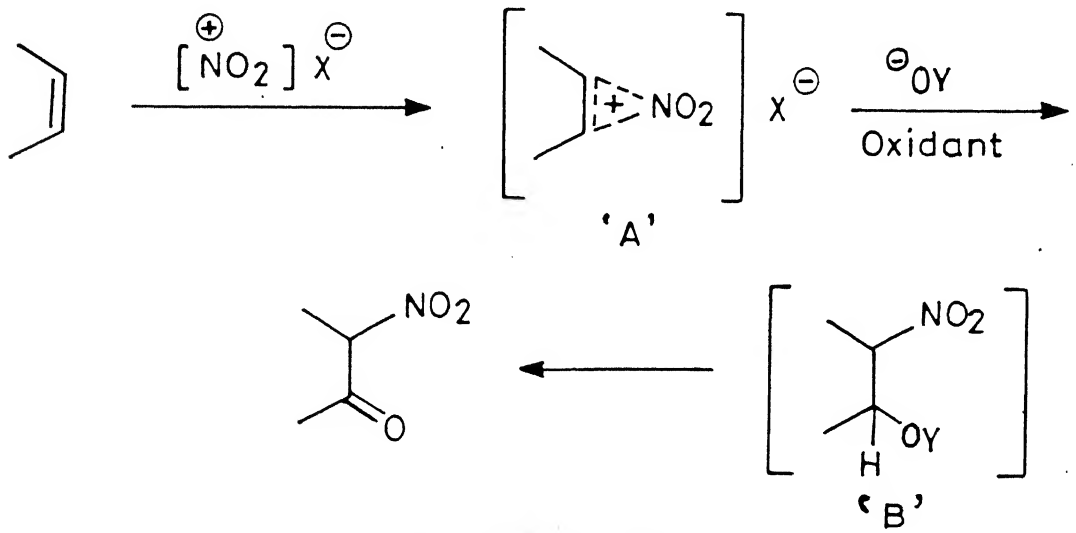
SCHEME - 20

II.B.2 RESULTS AND DISCUSSION

In the introduction part of this chapter, literature survey pertaining to the usefulness of α-nitroketones in organic synthesis has been delineated. Earlier in this chapter a number of methods for the synthesis of α-nitroketones are described. Although this literature survey reveals many methods for their preparation, each method has its own drawback(s). Full potential of these α-nitroketones has not been realized because of the limited availability of the satisfactory synthetic methods for their preparation. In our laboratory, studies related to the chemistry of nitro compunds has been an area of active investigation. For the first time 2-nitro and 3-nitro olefinic acetals have been prepared[44] and they have been utilised in the synthesis of α-methylene-γ-butyrolactones. Also α-nitroepoxides upon nucleophilic attack have been found to undergo facile ring opening to give many useful synthetic intermediates[45].

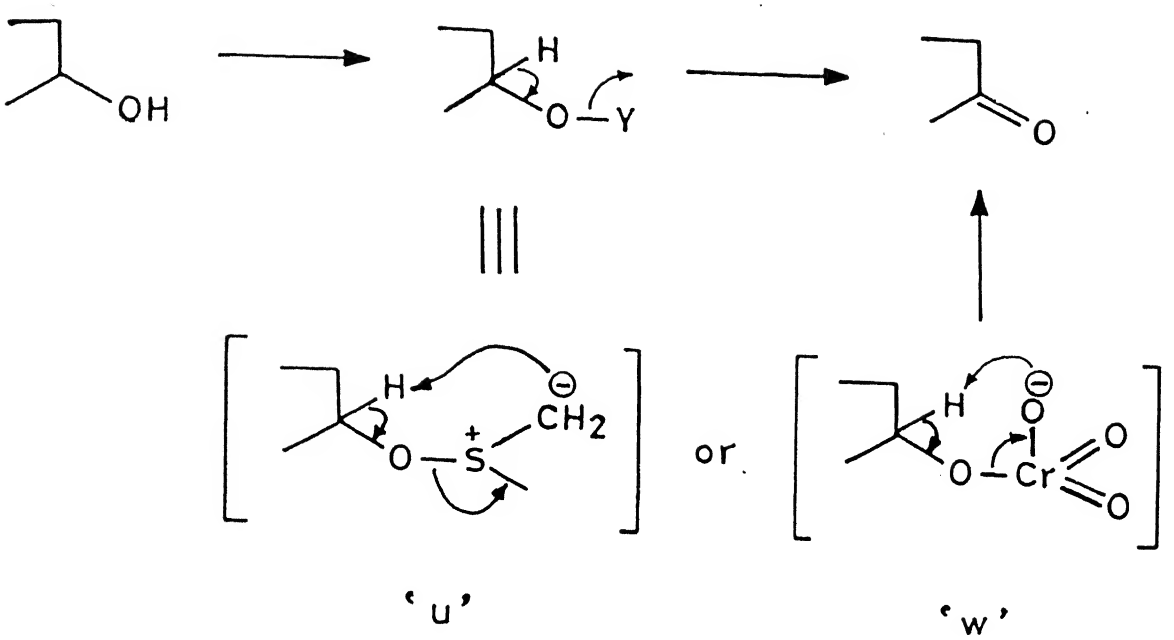
Our continued interest in the area of nitro chemistry led us to develop a new method for the preparation of α-nitroketones in a simple way. Most of the methods reported in the literature are based on the use of enol acetates or enol silyl ethers of the corresponding ketones of which the α-nitroketones need to be synthesised. There is only one report wherein olefins are directly converted into nitroketones and this utilises N_2O_4 as the reagent. Although this method of α-nitroketone preparation is being adopted, the use of N_2O_4 owing to its low boiling point (21^oC) is not always convenient especially if this has to be used

on a small scale in research laboratories. Further, this method is only applicable to cyclic olefins. Because of these reasons we were particulary interested in developing a simple method for the conversion of olefins into α-nitroketones which is (i) applicable to both cyclic as well as acyclic olefins and (ii) could be easily performed on samll scales. We reasoned that if a nitronium ion (NO_2^+) is allowed to react with olefins in conjunction with an oxidant, the corresponding α-nitroketones could be formed (cf. Scheme 21).



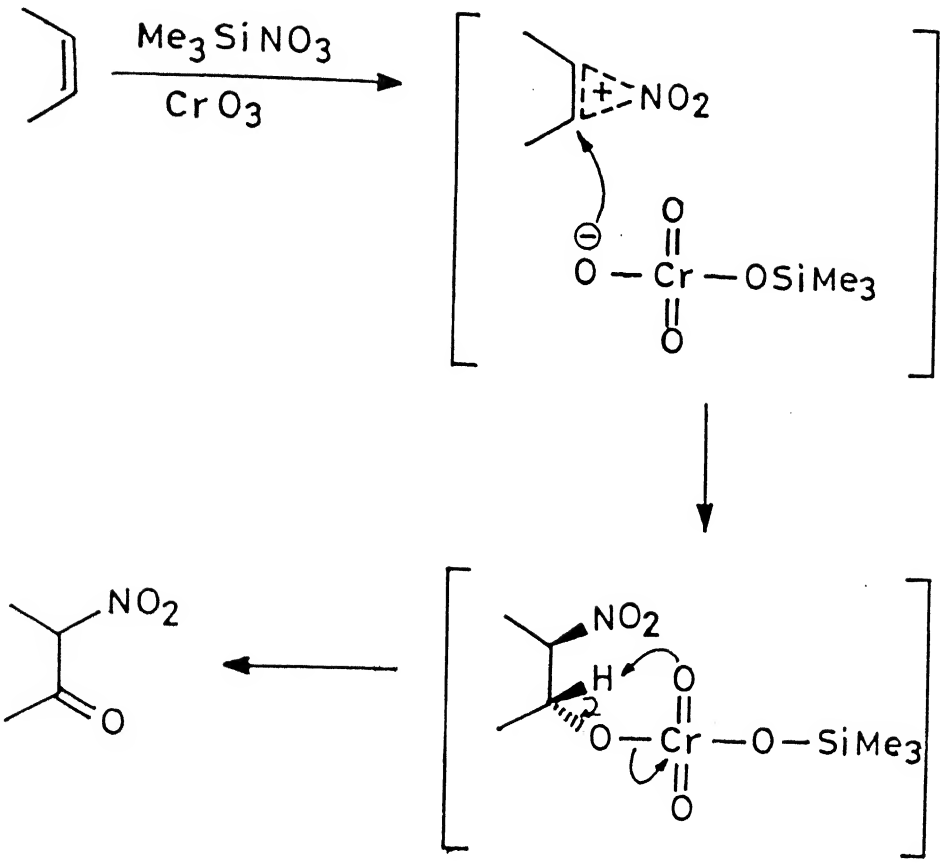
SCHEME - 21

In order to reduce this hypothesis in practice, it was however important to make sure that X^- i.e. the counterion of the NO_2^+ is not nucleophilic enough to attack the intermediate 'A' (Scheme 21). Also, the oxidant 'Y' is capable of oxidising in such a way as to give a keto group. For this, clearly 'Y' has to be linked to the olefin through an oxygen atom to form an intermediate 'U' or 'W' akin to the one which is usually present in the oxidation of alcohols (cf. Scheme 22).



SCHEME-22

Literature survey reveals that a good source of NO_2^+ is trimethylsilylnitrate[46] (Me_3SiONO_2) which is used to selectively nitrate polyols in the presence of a catalytic amount of $BF_3.Et_2O$. This can be easily prepared by a combination of Me_3SiCl and $AgNO_3$ in acetonitrile at 0^oC. We, therefore, selected to use this combination as a source of NO_2^+. It became immediately apparent that if one has to obtain an intermediate such as that in Scheme 22 (cf. 'U' or 'W'), there is now a competition between Me_3SiO^- and the oxidant. We chose CrO_3 as the oxidant hoping that a combination of Me_3SiONO_2 and CrO_3 should lead to the formation of $\left[Me_3SiO\text{-}\overset{\overset{O}{\|}}{\underset{\underset{O}{\|}}{Cr}}\text{-}O\text{-}NO_2 \right]$ which is still a source of NO_2^+ and now a modified, combined oxidant that is $Me_3SiO\text{-}\overset{\overset{O}{\|}}{\underset{\underset{O}{\|}}{Cr}}\text{-}O^-$ will serve the purpose we want (cf. Scheme 23).



SCHEME - 23

Indeed it was found that a variety of olefins react with the above combination of Me_3SiONO_2 and CrO_3 to give the corresponding α-nitroketones in excellent yields with the exception of α-nitrocyclopentanone (obtained in only 27%). The reaction is applicable to both cyclic as well as acyclic olefins. The results of the present study are recorded in Table 1. Typically, Me_3SiONO_2 was prepared by mixing $ClSiMe_3$ and $AgNO_3$ (1:1) in acetonitrile at 0^oC in dark under argon. The precipitated AgCl was removed by decantation after 1 hour. The acetonitrile solution of Me_3SiONO_2 was then added to the CrO_3 (1 mole

equivalent) solution in acetonitrile. After stirring at 15°C for 15 minutes, an olefin was added to it dropwise and stirring continued till the starting material was consumed (please see Table 1 for time). This led to the formation of α-nitroketones. In fact, Me_3SiONO_2 could be made as neat solution also upon reaction of $ClSiMe_3$ and $AgNO_3$ at -10°C without any solvent under dark. Reaction of this with CrO_3 and the olefin in CH_2Cl_2 was then attempted. Although the reaction does proceed to give the α-nitroketones, yields are not as good as when acetonitrile is used as the solvent. Interestingly, there was no need of any acid catalyst to trigger the reaction as it was reported for the nitration of polyols (cf. Ref. 46).

Cyclohexene 85 was converted into α-nitrocyclohexanone 95 in 61% yield when stirred for 24 hours with the above combination of reagents at room temperature. Its IR spectrum showed peaks at 1540 cm^{-1} corresponding to $-NO_2$, 1620 cm^{-1} for enolic -C=C-, and 1720 cm^{-1} corresponding to C=O. ^1H NMR spectrum showed signals at δ 4.83-5.18 (1H, t, $-\overset{|}{C}HNO_2$), 2.25-2.7 (4H, m, $-CH_2-CHNO_2-$, $-CH_2-\overset{O}{\overset{\|}{C}}-$), 1.35-2.17 (4H, m, $-CH_2-CH_2-$). Its mass spectrum had molecular ion peak M^+ at m/a 143, corresponding to the molecular weight of the compound. Its melting point was in accordance with the literature value.

Cycloheptene 86 gave a slightly better yield (70%) of α-nitrocycloheptanone 96. Reaction of cyclopentene 84 was found to be relatively unclean. It gave only 27% yield of α-nitrocyclopentanone 94 under the reaction conditions. It is not surprising that the yield of 94 was less as is known in the

literature that α-nitrocyclopentanones are very labile and they undergo ring cleavage[47].

On the other hand, α-nitrocyclododecanone 97 was formed in very good yield of 79% from cyclododecene 87. 97 was fully characterised by IR and NMR spectral data. Its IR spectrum showed peaks at 1540 cm^{-1} and 1710 cm^{-1} corresponding to $-NO_2$ and C=O groups respectively. ^1H NMR spectrum indicated signals at δ 4.9-5.16 (1H, t, $-\overset{|}{C}HNO_2$), 2.21-2.6 (4H, m, $-CH_2-CHNO_2$, $-CH_2-\overset{|}{C}=O$), 1.1-2.1 (16H, m, aliphatic) and its melting point was 75°C which matched with the literature value of 77-77.5°C [48].

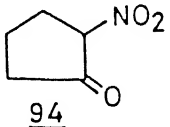
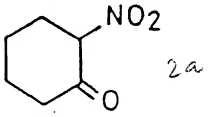
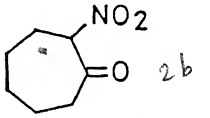
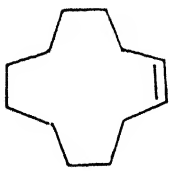
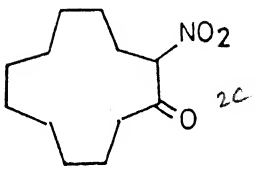
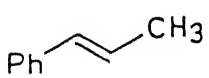
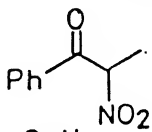
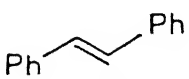
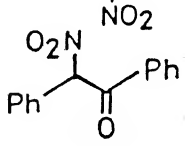
After successfully testing the reactivities of cyclic olefins, we diverted our attention to acyclic olefins. They underwent much cleaner reactions when compared to the cyclic olefins and the products were isolated in excellent yields with aliphatic acyclic olefins (cf. entries 5, 6 and 7; Table 1). The reaction has also been found to be highly regioselective. Addition takes place in Markownikoff fashion giving the more stable carbonium ion. Thus, when 1-hexene 88 was treated with this reagent system 1-nitro-2-hexanone 98 was formed in 88% yield. Its IR spectrum showed signals at 1540 and 1720 cm^{-1} corresponding to $-NO_2$ and C=O groups respectively. ^1H NMR spectrum showed signals at δ 5.17 (2H, s, $-CH_2NO_2$), 2.4-2.68 (2H, t, $-CH_2-\overset{|}{C}=O$), 1.1-1.6 (7H, m, aliphatic). Likewise, 1-dodecene 89 gave 1-nitro-2-dodecanone 99 in 94% yield as the only regioisomer. 1-Tridecene 90 also gave only one isomer i.e., 1-nitro-2-tridecanone 100 in 81% yield. Both these compounds have been fully characterised by their IR and NMR spectral data. Mass spectrum of 99 showed molecular ion peak at 229 which corresponds

to its molecular weight. Both 99 and 100 are nice crystalline solids whose m.p. are recorded (cf. Experimental section).

When phenyl substituted olefins were made to react with this reagent system, conversion to α-nitroketones took place quite smoothly without any aromatic nitration. β-Methylstyrene 91 gave α-nitropropiophenone 101 in 76% yield. Only this regioisomer was isolated as expected, since the more stable benzylic cation dictated the reaction. Its IR spectrum showed peaks at 1550 and 1680 cm^{-1} corresponding to $-NO_2$ and C=O groups respectively. Its ^1H NMR spectrum showed signals at δ 7.85-8.13 (2H, m, aromatic), 7.25-7.68 (3H, m, aromatic), 5.9-6.35 (1H, q, $CH_3\underline{C}\underline{H}NO_2$), 1.85-2.0 (3H, d, $C\underline{H}_3CHNO_2$). Likewise, 1-nitro-1,2-diphenyl ethanone 102 was formed in 79% yield from trans-stilbene (92) which was characterised fully based on its IR and NMR spectral data. In this reaction, however, 7% benzaldehyde was formed due to C-C bond cleavage.

In conclusion we believe that the present method affords an easy, efficient, high yielding and a general method of preparing α-nitroketones from olefins. It would be more useful if the present reagent system is applied to more complicated olefins and utilised in the synthesis of natural products.

Table 1

Entry	Olefin	Nitroketone	Time (hr)	Yield (%)
1	84	 94	24	27
2	1a 85	 2a 95	24	61
3	1b 86	 2b 96	24	70
4	 1c 87	 2c 97	24	72
5	$CH_3(CH_2)_3CH=CH_2$ 1d 88	$CH_3(CH_2)_3\overset{O}{\overset{\|}{C}}-CH_2NO_2$ 98 2d	24	88
6	$CH_3(CH_2)_9CH=CH_2$ 1e 89	$CH_3(CH_2)_9\overset{O}{\overset{\|}{C}}-CH_2NO_2$ 99 2e	24	94
7	$CH_3(CH_2)_{10}CH=CH_2$ 1f 90	$CH_3(CH_2)_{10}\overset{O}{\overset{\|}{C}}-CH_2NO_2$ 100 2f	20	81
8	 91	 101	10	76
9	 92	 102	10	79

II.B.3 EXPERIMENTAL

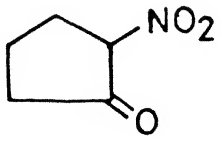
General

All the reagents and solvents were purified according to earlier methods described in Section I.A.3.

General Experimental Procedure for the Conversion of Olefins to α-Nitroketones with Me_3SiONO_2-CrO_3 Reagent System :

To a stirred solution of Me_3SiCl (132 mg, 1.2 mmol) in 2 ml CH_3CN was added $AgNO_3$ (204 mg, 1.2 mmol) in dark at 0^oC under argon atmosphere and reaction mixture was stirred for 30 min. during which period AgCl precipitated out. The acetonitrile solution of the resulting trimethylsilylnitrate was added to a solution of CrO_3 (150 mg, 1.5 mmol) in 1 ml of CH_3CN and it was further stirred for 15 min. at 15^oC. To this reaction mixture, 1 mmol of an olefin was added very slowly and dropwise. Fast addition was found to lead to highly exothermic and vigorous reaction. In case where the olefin was insoluble in CH_3CN, 1 ml of dichloromethane was added to the reaction mixture. The reaction mixture was further stirred after the addition of olefin for the time mentioned in Table 1. The reaction mixture was then treated with water (10 ml) and thorougly extracted with Et_2O (3x15 ml). The combined ethereal layer was washed with brine solution (20 ml) and dried over anhydrous Na_2SO_4. Evaporation of the organic layer on a rotary evaporator gave fairly pure α-nitroketones in good yields, which were further purified by column chromatography [eluent : petroleum ether-ethyl acetate].

α-Nitrocyclopentanone 94

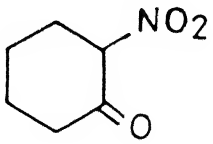


Yield : 26%

IR spectrum (neat) ν_{max} : 1530 ($-NO_2$), 1620 (C=C), 1680 (C=O) cm^{-1}.

^1H NMR spectrum (CCl_4) : δ 1.4-2.23 (2H, m, $-CH_2$), 2.3-2.7 (4H, m, $-CH_2-CHNO_2$, $-CH_2-C(=O)$), 4.35-4.9 (1H, t, $-CHNO_2$).

α-Nitrocyclohexanone 95



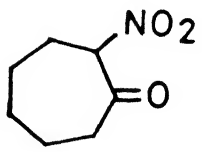
Yield : 61%

IR spectrum (neat) ν_{max} : 1540 ($-NO_2$), 1620 (C=C), 1725 (C=O) cm^{-1}.

^1H NMR spectrum (CCl_4) : δ 1.35-2.17 (4H, m, $-CH_2-CH_2-$), 2.25-2.7 (4H, m, $-CH_2-CH-NO_2-$, $-CH_2-C(=O)$), 4.83-5.18 (1H, t, $-CH-NO_2$).

Mass spectrum : 143 (M^+).

α-Nitrocycloheptanone 96

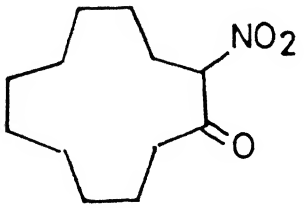


Yield : 70%

IR spectrum (neat) ν_{max} : 1550 ($-NO_2$), 1610 (C=C), 1720 (C=O) cm^{-1}.

^1H NMR spectrum (CCl_4) : δ 1.52-2.17 (8H, m, $4X-CH_2$), 2.34-2.85 (2H, m, $-CH_2-\overset{|}{C}=O$), 5.08-5.36 (1H, t, $-\overset{|}{C}HNO_2$).

α-Nitrocyclododecanone 97



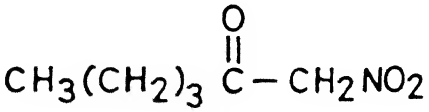
Yield : 72%

m.p. : 75°C.

IR spectrum (CCl_4) ν_{max} : 1540 ($-NO_2$), 1710 (C=O) cm^{-1}.

^1H NMR spectrum (CCl_4) : δ 1.1-2.1 (16H, m, $8X-CH_2$), 2.21-2.26 (4H, m, $-CH_2-\overset{|}{C}HNO_2$, $-CH_2-\overset{|}{C}=O$), 4.9-5.16 (1H, t, $-\overset{|}{C}HNO_2$).

1-Nitro-2-hexanone 98

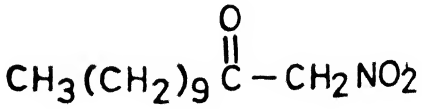


Yield : 88%

IR spectrum (neat) ν_{max} : 1540 ($-NO_2$), 1720 (C=O) cm^{-1}

^1H NMR spectrum (CCl_4) : δ 1.1-1.6 (7H, m, aliphatic), 2.4-2.68 (2H, t, $-CH_2-\overset{|}{C}=O$), 5.17 (2H, s, $-CH_2-NO_2$).

1-Nitro-2-dodecanone 99



Yield : 94%

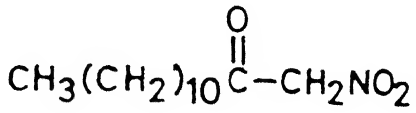
m.p. : 79°C

IR spectrum ($CHCl_3$) ν_{max} : 1550 ($-NO_2$), 1725 (C=O) cm^{-1}.

^1H NMR spectrum ($CDCl_3$) : δ 0.9-1.5 (19H, m, aliphatic), 2.2-2.5 (2H, t, $-CH_2-\overset{|}{C}=O$), 5.18 (2H, s, $-CH_2NO_2$).

Mass spectrum : 229 (M^+)

1-Nitro-2-tridecanone <u>100</u>



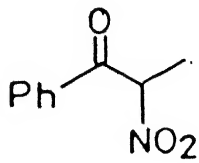
Yield : 81%

m.p. : 84°C

IR spectrum ($CHCl_3$) ν_{max} : 1550 ($-NO_2$), 1720 (C=O) cm^{-1}

^1H NMR spectrum ($CDCl_3$) : δ 0.8-1.5 (21H, m, aliphatic), 2.2-2.5 (2H, t, $-CH_2-\overset{|}{C}=O$), 5.18 (2H, s, $-CH_2-NO_2$)

α-Nitropropiophenone <u>101</u>

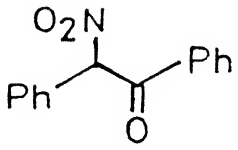


Yield : 76%

IR spectrum (neat) ν_{max} : 1550 ($-NO_2$), 1680 (C=O) cm^{-1}.

^1H NMR spectrum (CCl_4) : δ 1.85-2.0 (3H, d, $-\overset{|}{C}H-C\underline{H}_3$, J=6Hz), 5.9-6.35 (1H, q, $-\overset{|}{C}\underline{H}-CH_3$), 7.25-7.68 (3H, m, aromatic), 7.85-8.13 (2H, m, aromatic)

1-Nitro-1,2-diphenylethanone 102



Yield : 79%

m.p. : 74-75°C.

IR spectrum ($CDCl_3$) ν_{max} : 1550 ($-NO_2$), 1680 (C=O) cm^{-1}.

^1H NMR spectrum ($CDCl_3$) : δ 7.15 (1H, s, $-\overset{|}{C}HNO_2$), 7.25-7.60 (8H, m, aromatic), 7.8-8.0 (2H, m, aromatic).

II.B.4 REFERENCES

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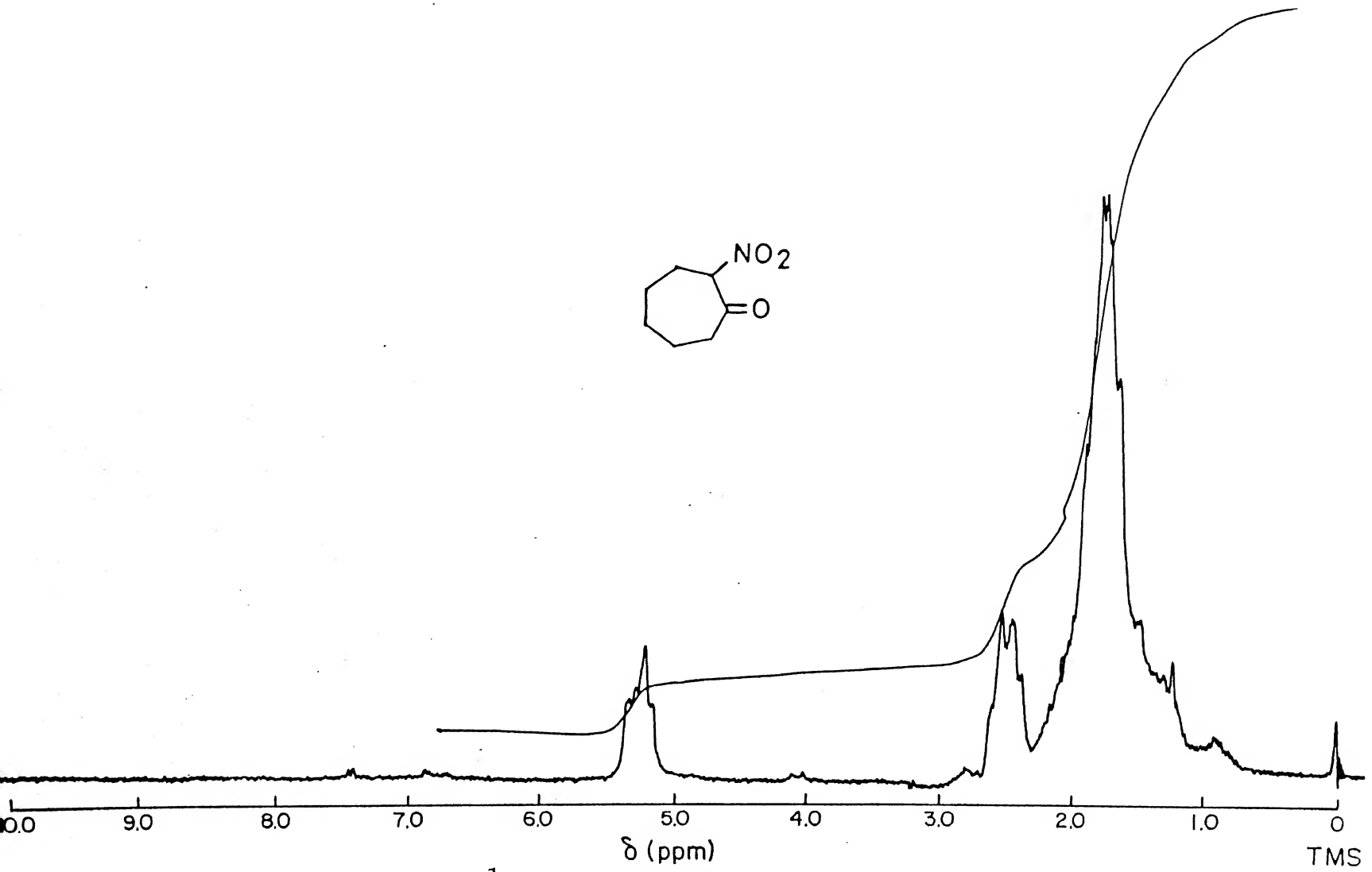
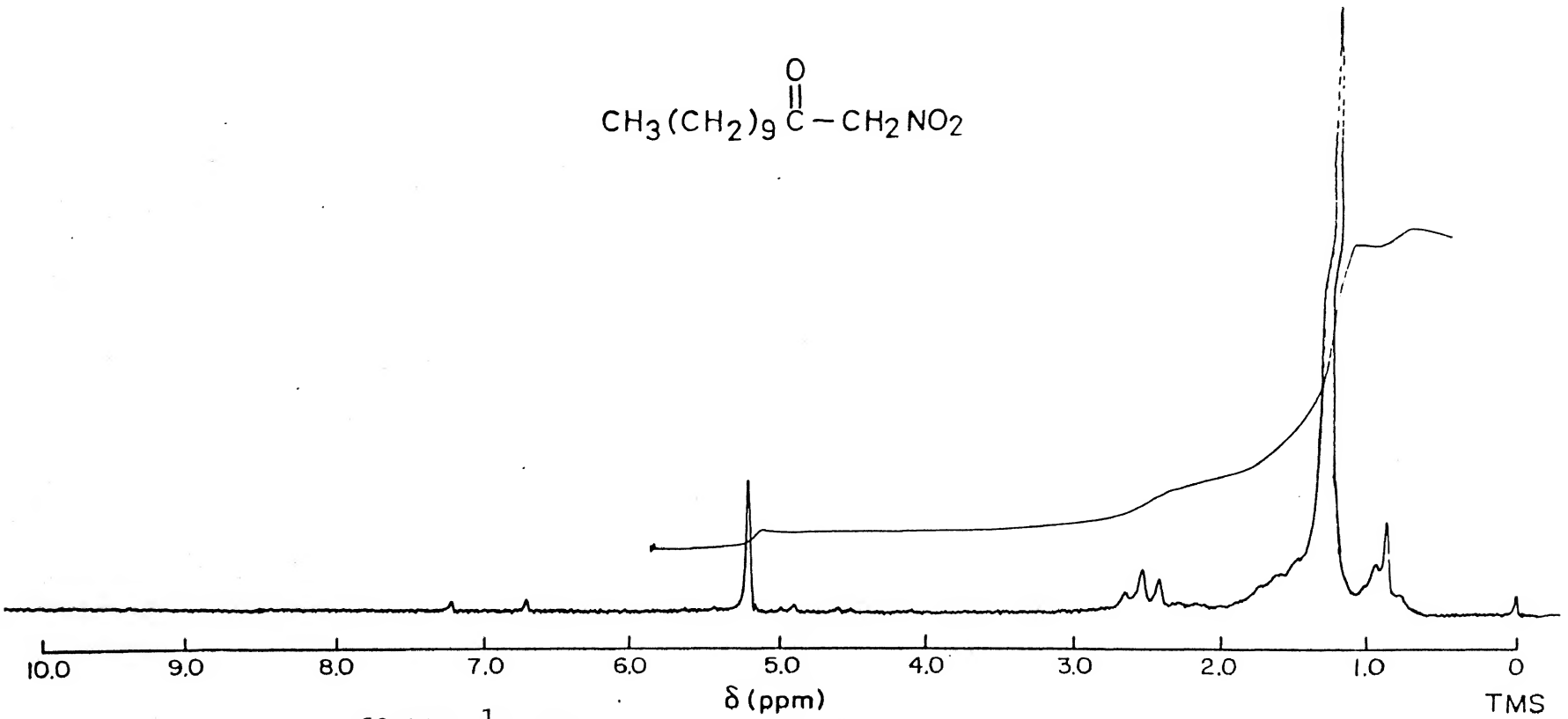
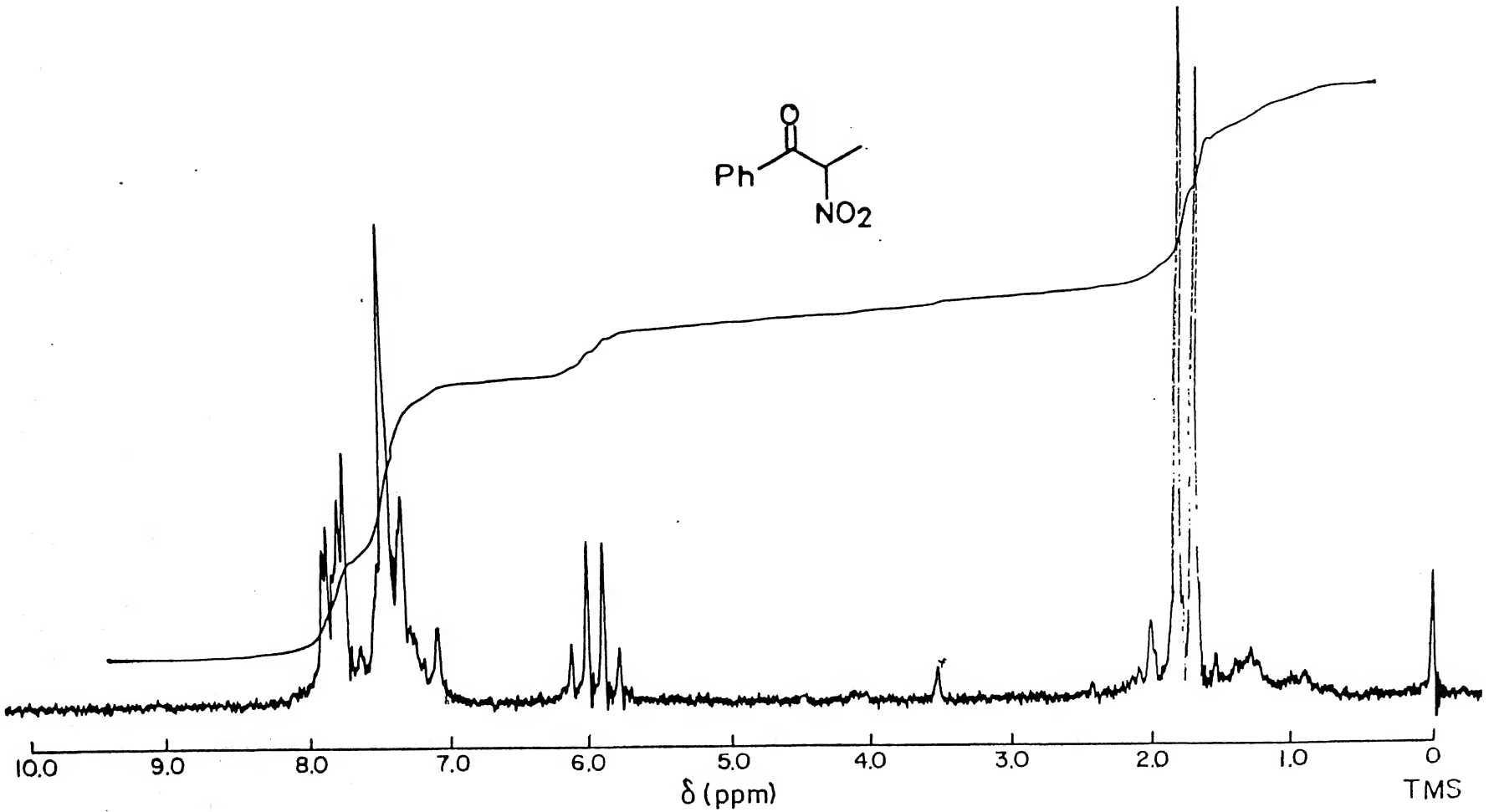


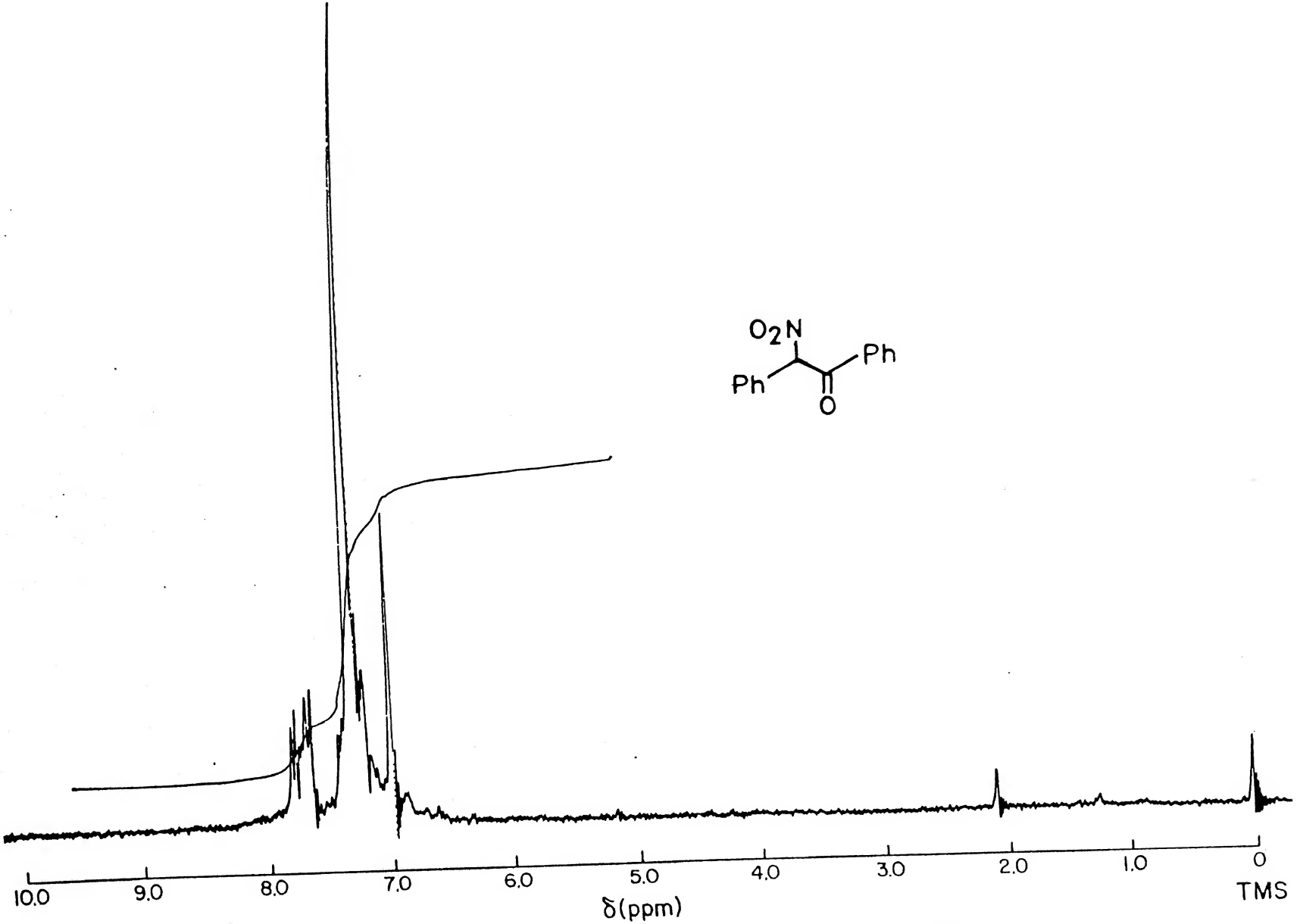
60 MHz ^{1}H NMR spectrum of the compound 96



60 MHz ^{1}H NMR spectrum of the compound 99



60 MHz ^{1}H NMR spectrum of the compound 101



60 MHz ^{1}H NMR spectrum of the compound 102

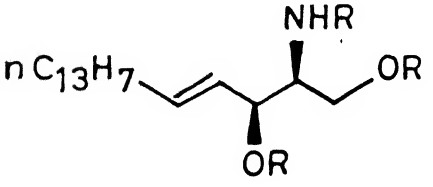
CHAPTER II

PART C

ONE STEP SYNTHESIS OF α-AZIDOKETONES FROM OLEFINS WITH TRIMETHYLSILYLAZIDE-CHROMIUM TRIOXIDE REAGENT SYSTEM

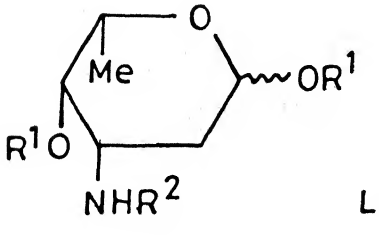
II.C.1 INTRODUCTION

The chemistry of azides has attracted the attention of chemists since the discovery of Phenacyl azide by Griess[1] over 100 years ago. Since then the growth of its chemistry has been so much that many reviews and books have been published from time to time. Some of the important ones deal with acyl azides[2], alkyl azides[3], silyl azides[4(i)], vinyl azides[4(ii)], and 1,2,3-triazoles[4(iii),(iv)] etc. Although α-azido carbonyl compounds have been known to be useful intermediates, their synthetic utility has not been well recognised and very few systematic studies regarding their preparation and utility have been performed. These α-azido ketones could be useful precursors for many natural and unnatural products as the azido group could be easily transformed into an amine group and the keto group into an alcohol. Thereby, vicinal amino alcohols can be obtained from α-azido ketones. These vicinal amino alcohols are found in a variety of important compounds such as Sphingosine[5] A and L-Daunosamine[6] B which is a potential anticancer drug (Fig I).



R = H
R = Ac

A Sphingosine

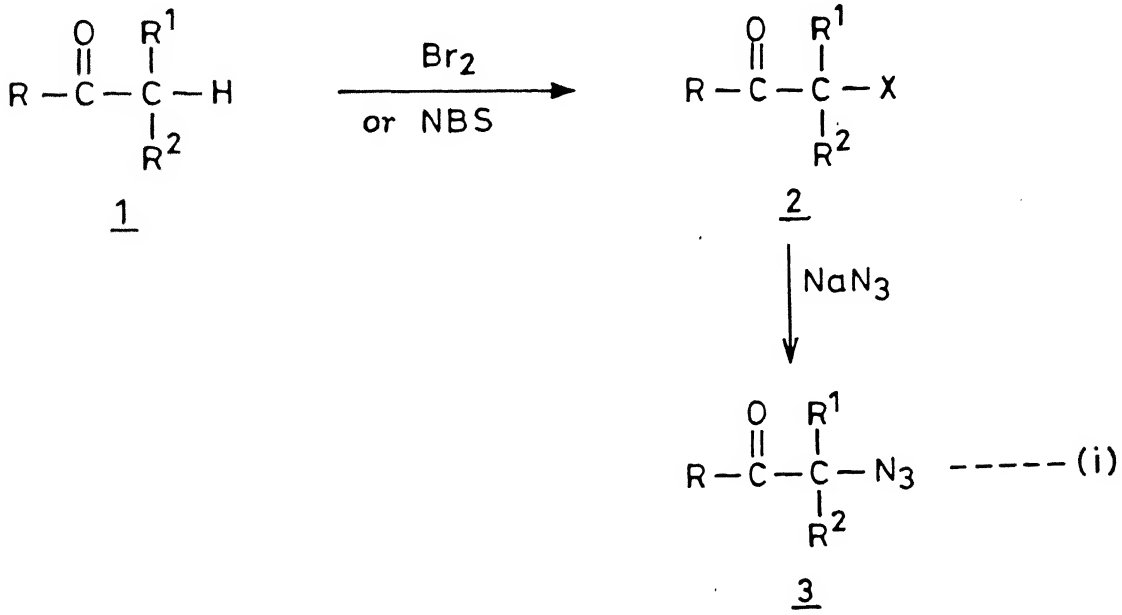


$R^1 = R^2 = H$

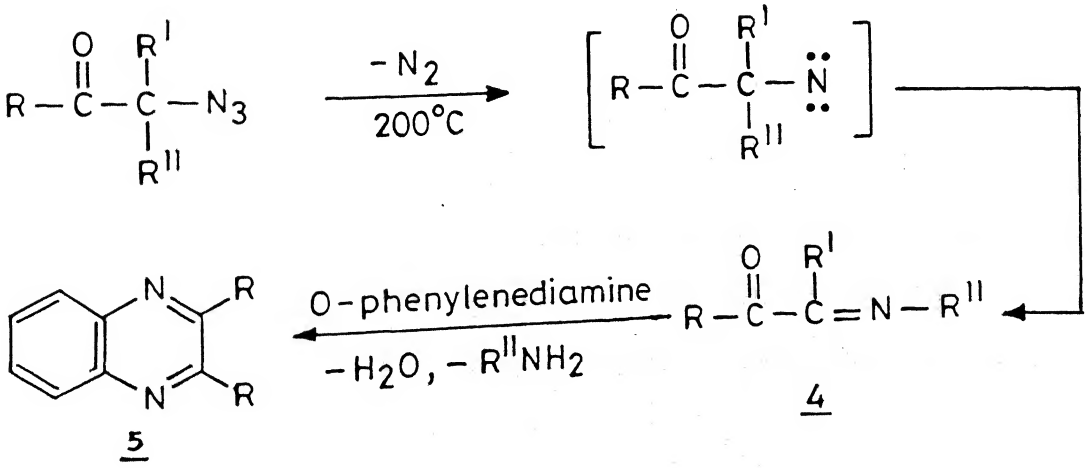
L - Daunosamine

In the following pages, literature reports on the synthesis and utility of α-azido ketones are described in brief.

α-Azido ketones are prepared[7] either from the corresponding carbonyl compounds or from the α-hydroxy carbonyl compounds. Transformation into the α-halo derivatives has been carried out by standard methods of bromination of carbonyl compounds using bromine or N-bromo succinimide, or by treating α-hydroxy carbonyl compounds with thionyl chloride. The displacement of halogen by $N_3^{\ominus}$ furnishes the α-azido carbonyl compounds (equation (i), Scheme 1).



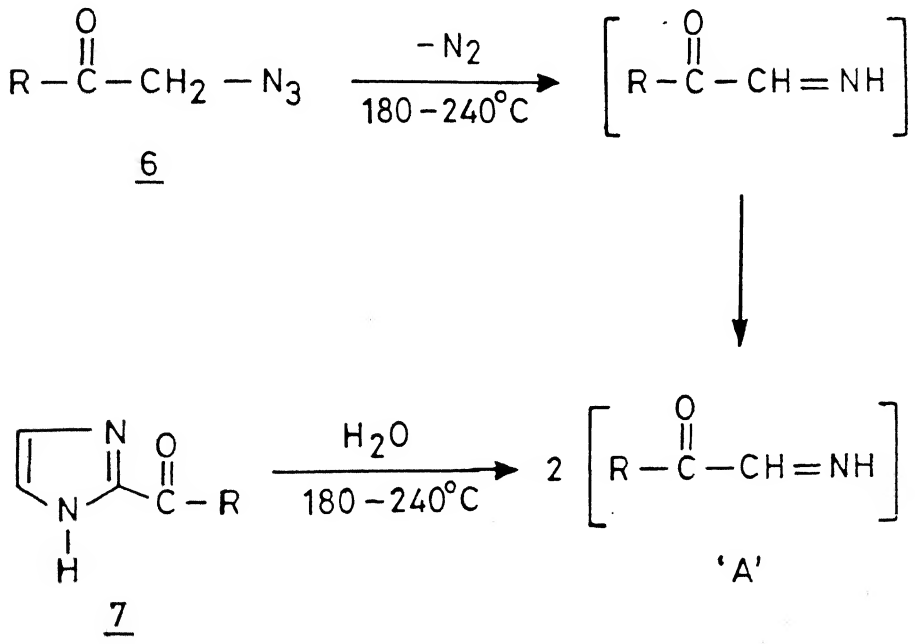
1 2 3



4 5

These α-azido carbonyl compounds are converted to Quinoxalines 5 by heating at 200°C in the presence of o-phenylenediamine (equation (ii), Scheme 1).

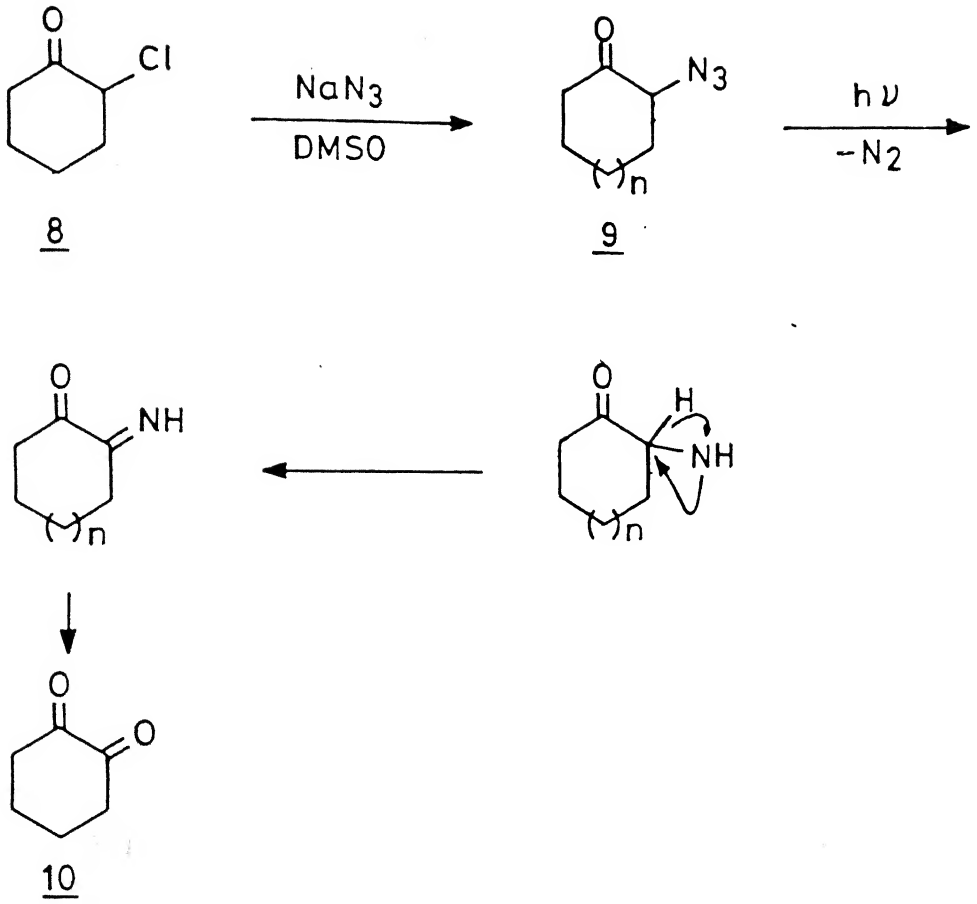
Phenacyl azides 6 and structurally related compounds undergo the loss of N_2 molecule when heated between 180-240°C in an inert solvent. Good yields of the corresponding imidazoles 7 result[8] from dimerisation and dehydration of the postulated α-imino ketone intermediates A (cf. Scheme 2).



R = C_6H_5 , p Br − C_6H_4 , β-$C_{10}H_7$

SCHEME -2

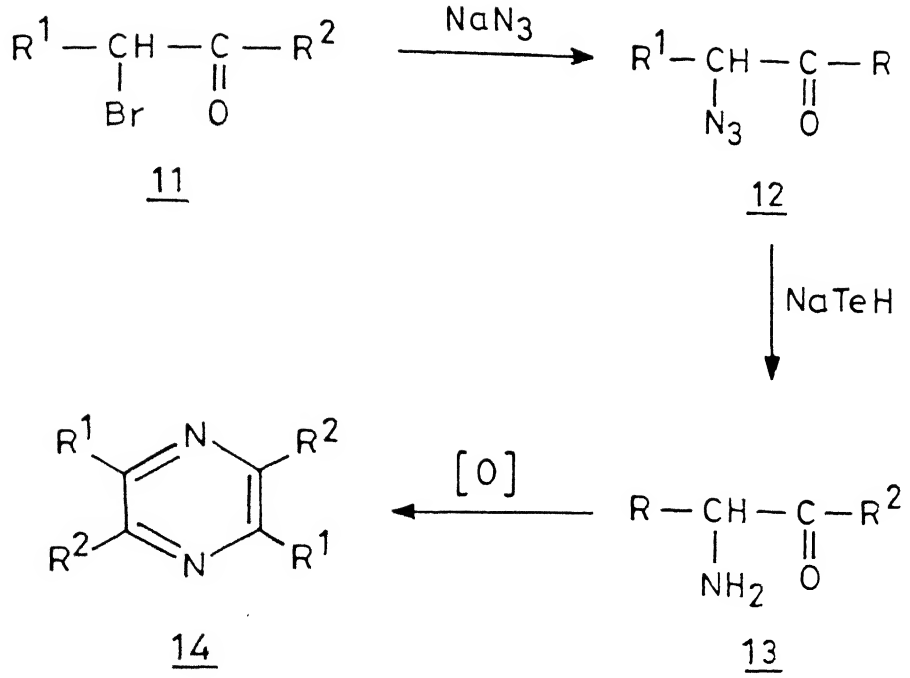
When α-azido ketones are irradiated, loss of N_2 molecule occurs resulting in the formation of α-imino ketones. These upon acid hydrolysis give the corresponding 1,2-diketones[9] 10 (Scheme 3).



SCHEME-3

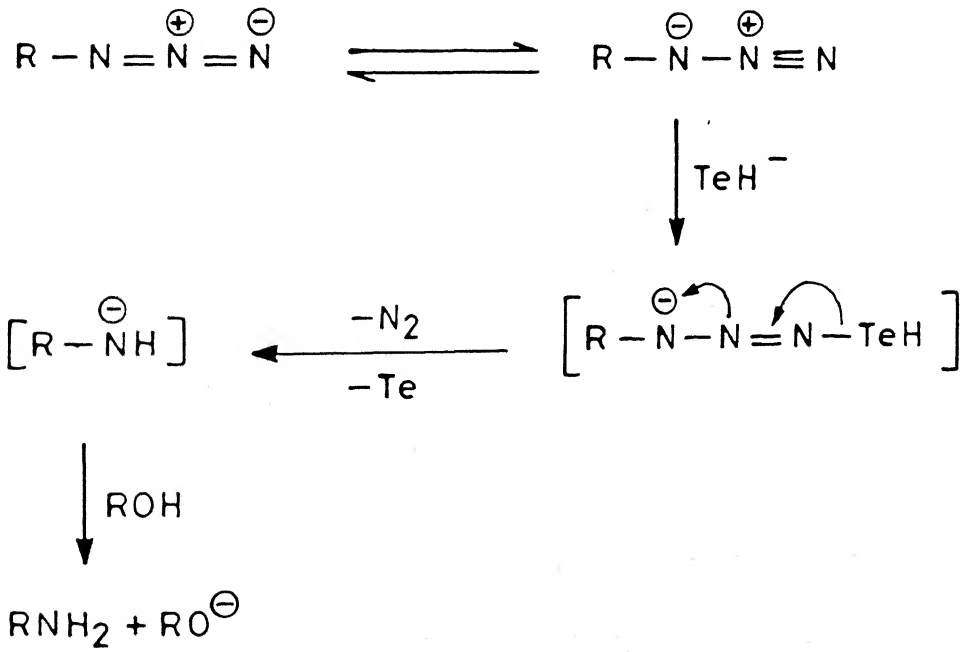
α-Azido ketones 12, when treated with sodium hydrogen telluride in ethanol at room temperature, are easily converted to pyrazines[10] 14 via the self condensation of the initially formed α-amino ketone 13 followed by aerobic oxidation during the workup (Scheme 4).

Conversion of an azide to amine may be explained by a pathway which involves the attachment of hydrogen telluride anion to the terminal nitrogen atom of the azido group followed by the fragmentation of the resulting triazene type adduct in a way as shown below (Scheme 5).



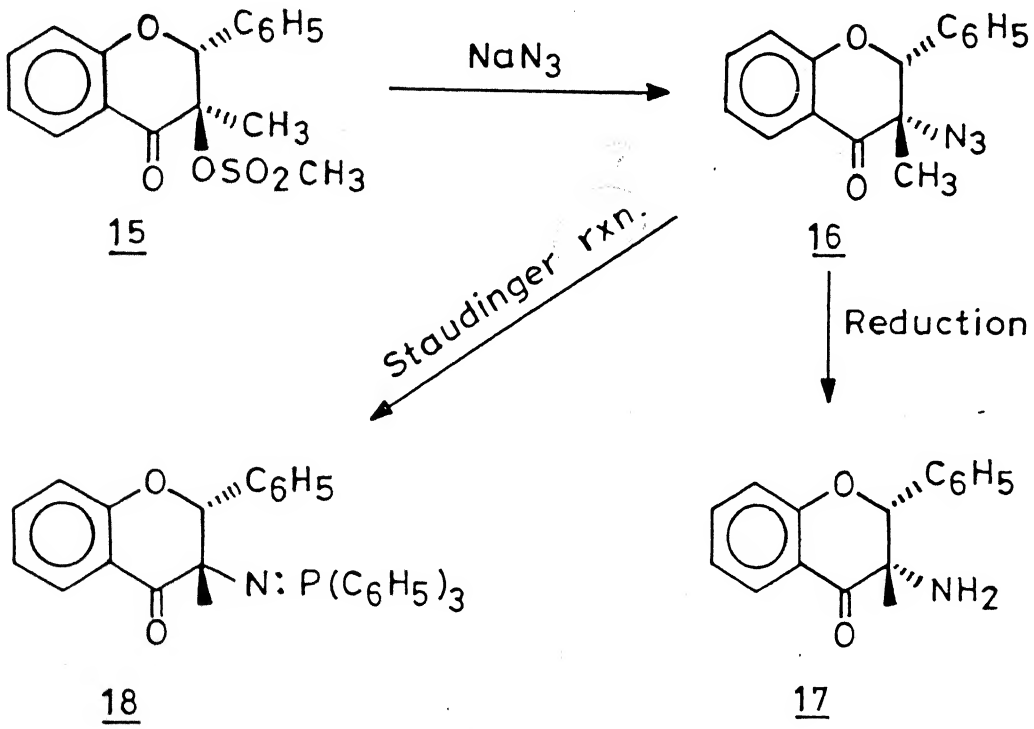
11 12 13 14

SCHEME - 4



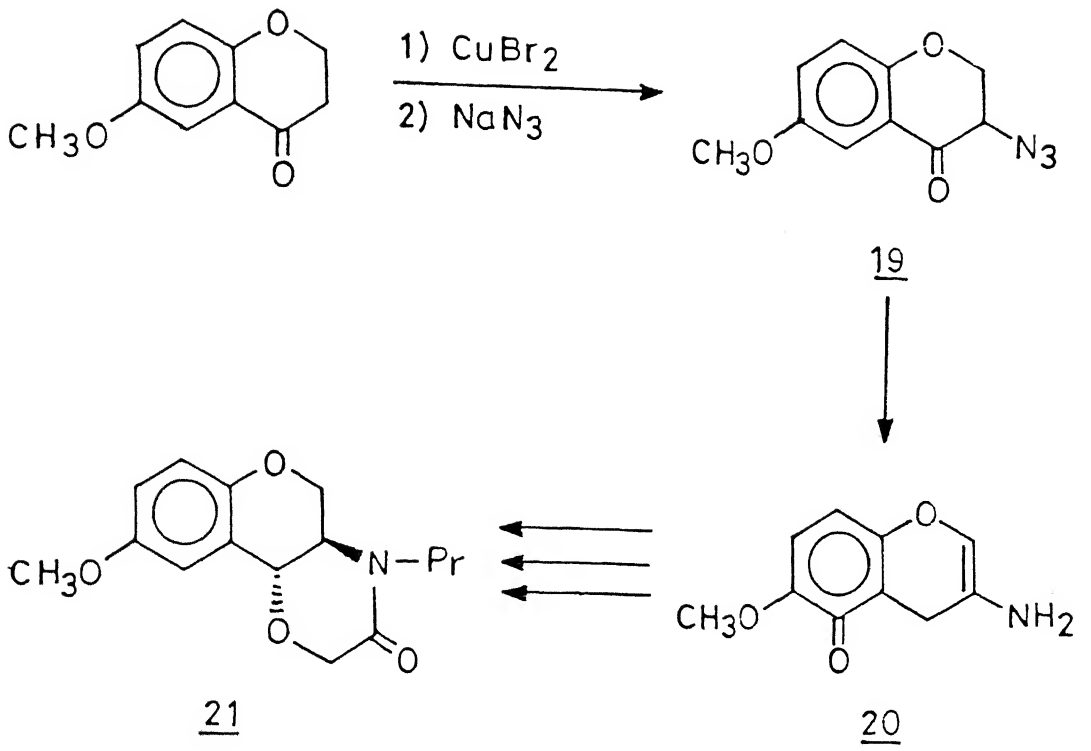
SCHEME - 5

α-Azido ketones are used in the flavanoid chemistry also[11]. Thus, 2,3-dihydro-t-3-mesyloxy-c-3-methyl-γ-2-phenyl-4H-1-benzopyran-4-one 15 when treated with NaN_3 gives 3-azido-2,3-dihydro-t-methyl-γ-2-phenyl-4H-1-benzopyran-4-one 16 in good yield. Selective reduction of the azido group led to the formation of 3-amino-2,3-dihydro-t-3-methyl-γ-2-phenyl-4H-1-benzopyran-4-one 17. On the other hand, Staudinger reaction yields the expected imino phosphorane 18 (Scheme 6).



SCHEME - 6

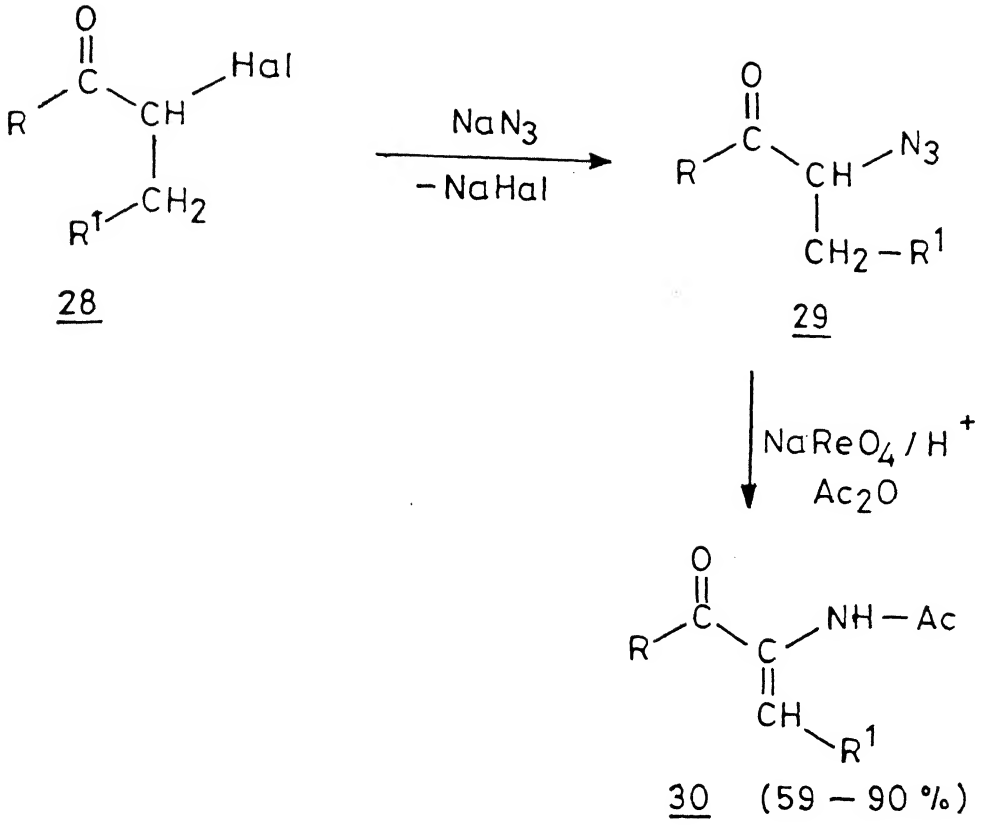
Synthesis of Ergoline 21, which is a dopamine agonist has been demonstrated using an appropriate α-azido ketone[12] 19 (Scheme 7).



SCHEME - 7

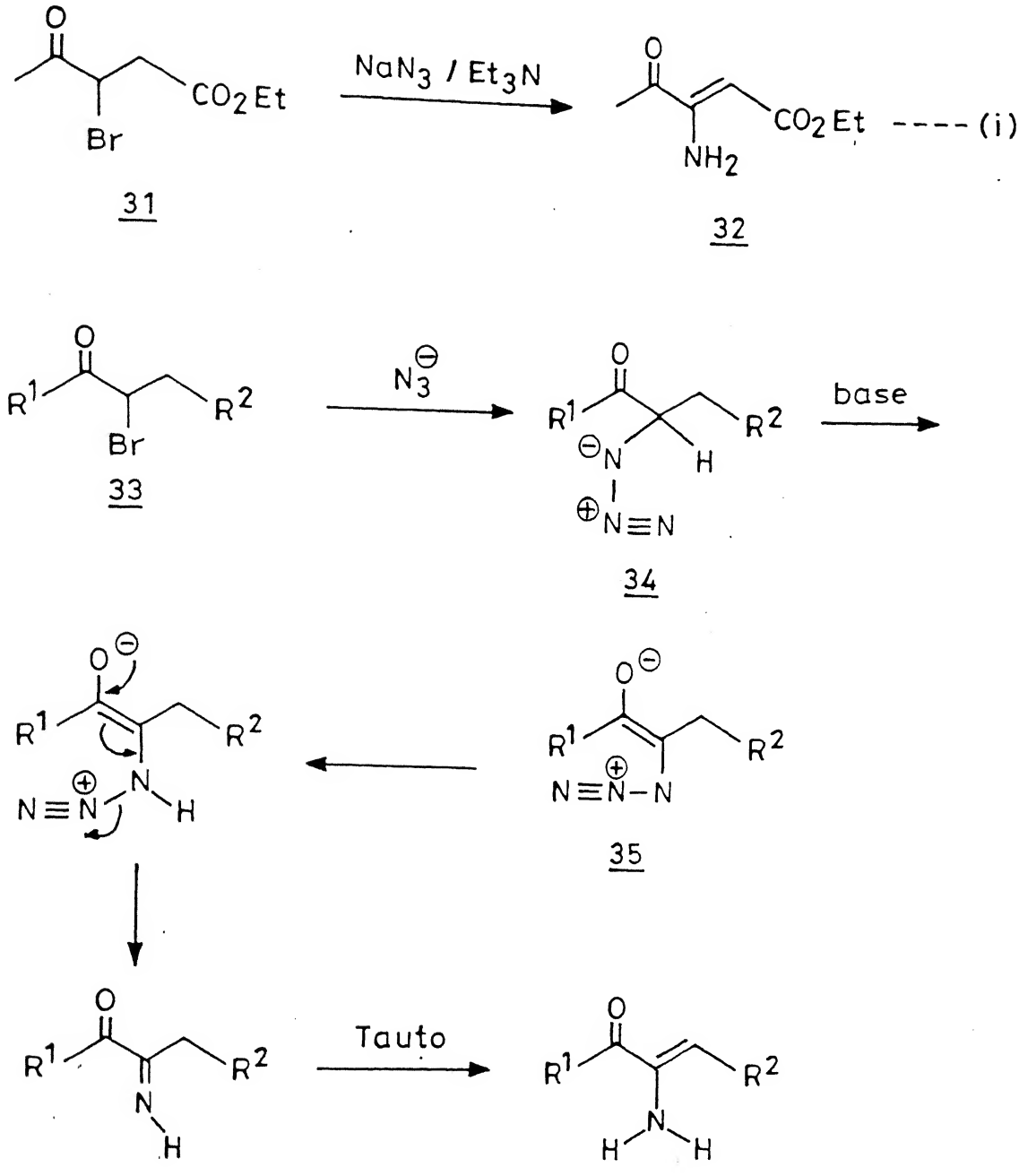
α-Azido ketones are converted to 2-(acetylamino)-2-alken-1-ones in good yield by perrhenate catalysts[13]. The thermally induced elimination of N_2 from cyclic and acyclic α-azido ketones is accelerated by catalytic amount of perrhenate in acetic anhydride and in the presence of small amounts of mineral acid, if necessary (Scheme 8).

α-Enamino ketones, which are useful synthetic intermediates, could be prepared by the reaction of NaN_3 with α-bromoketones in the presence of a base like Et_3N [14] (equation (i), Scheme 9). The mechanism proceeds via the formation of α-azido ketones 34 (Scheme 9).



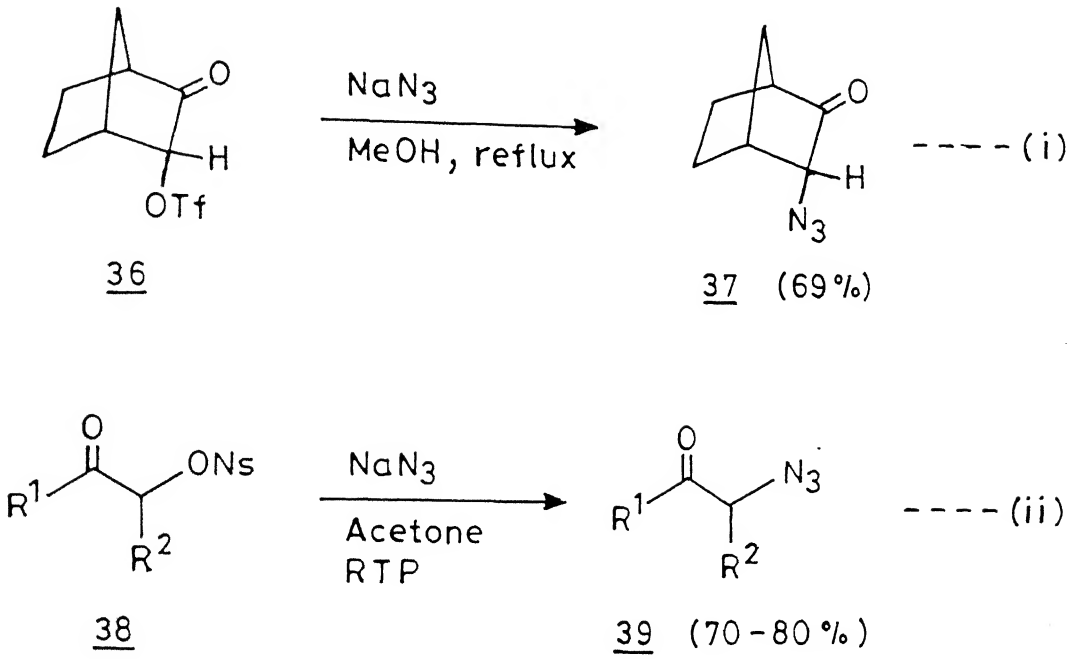
	a	b	c	d	e
R	I	I	I	Ph	CH_3
	CH_2	CH_2	CH_2		
R^1	I	I	I	H	H

SCHEME – 8



SCHEME - 9

In most of the cases as described above, α-azido ketones have been obtained by the replacement of an α-halogen with $N_3^{\ominus}$. Improvement in such displacements has led to the use of o-triflates[15] as the leaving group (equation (i), Scheme 10). Likewise, nosylates have been found to be better than triflates in the synthesis of azido ketones[16] (equation (ii), Scheme 10).

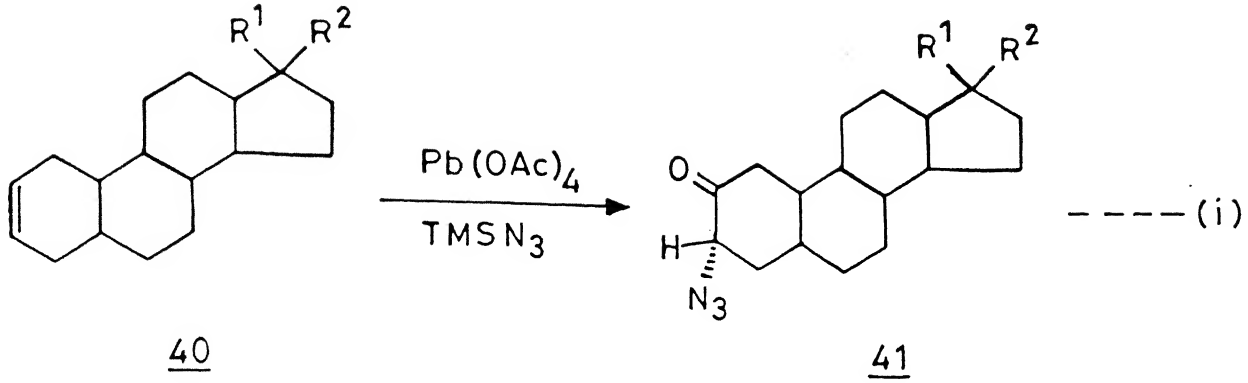


SCHEME-10

Zbiral and Nestler[17] have reported the synthesis of α-azido ketones from olefins. They have found that the reaction of the two fold branched steroidal olefins with the $Pb(OAc)_4$-$TMSN_3$ reagent system below -20°C yields α-azido ketones with the azido group at the axial position (equation (i), Scheme 11).

Further, in their studies Ehrenfreund and Zbiral[18] have found that (diacetoxyiodo)benzene-$TMSN_3$ is yet another reagent system which gives α-azido carbonyl compounds, from olefins. Thus, various cyclo and bridged olefins are transformed into the corresponding α-azido ketones (equation (ii) and (iii), Scheme 11).

On the other hand, when conjugated steroidal enones were

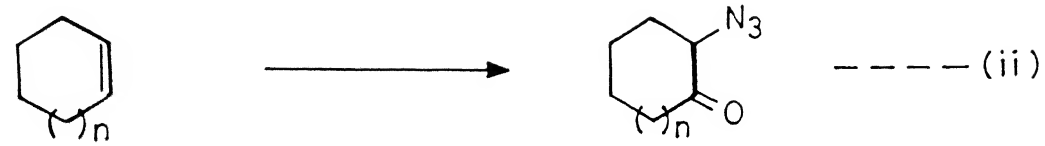


40 ----(i)---- 41

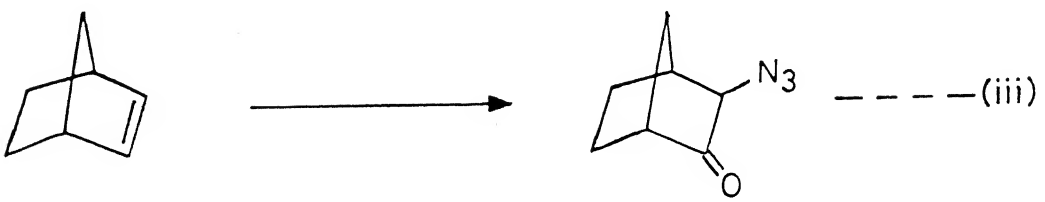
1) $R^1 = H$, $R^2 = C_8H_{17}$

2) $R^1 = R^2 = O$

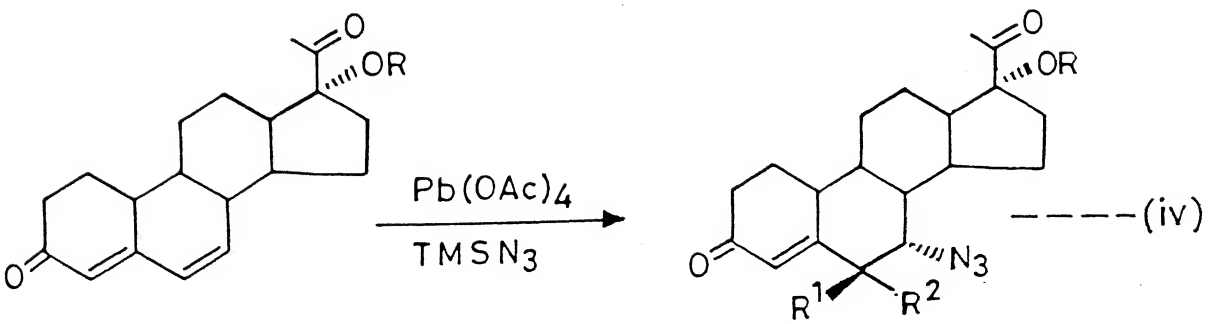
3) $R^1 = R^2 = O$



42 ----(ii)---- 43 (95%)



44 ----(iii)---- 45 (39%)



46 ----(iv)---- 47

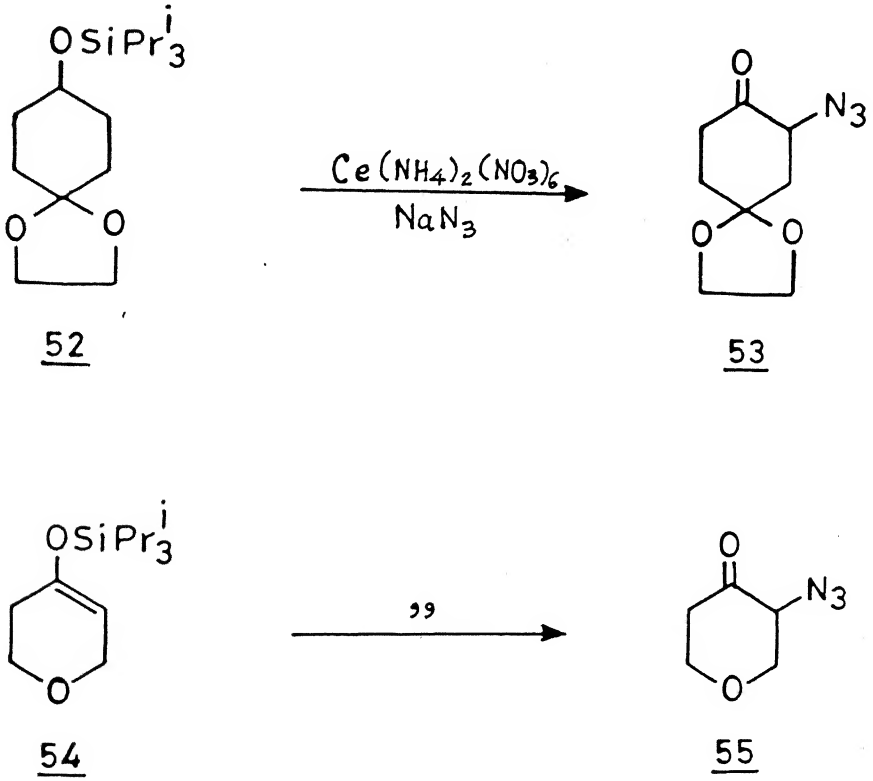
$R^1 = N_3$ $R^2 = H$ (55%)

$R^1 = R^2 = O$ (24%)

SCHEME - 11

treated with the combination of $Pb(OAc)_4$-$TMSN_3$ (in the ratio of 1:4), only 24% α-azido ketone compounds were formed along with the major diazide compound[19] (equation (iv) Scheme 11).

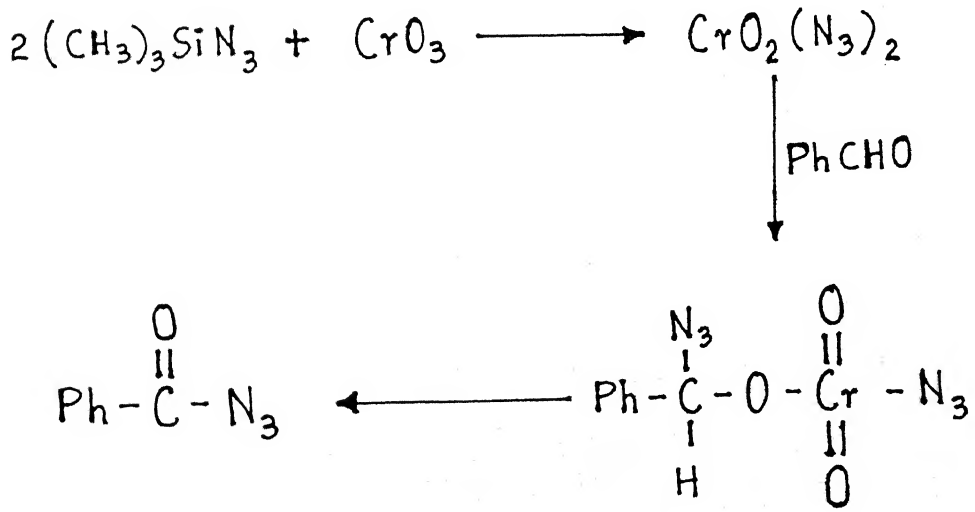
Recently, Magnus and Barth[20] have reported a very interesting approach to α-azido ketones. Thus, treatment of triisopropyl silyl enol ethers with ceric ammonium nitrate/NaN_3 at -20°C in CH_3CN gives α-azido ketones in average to good yields (Scheme 12). Triisopropyl silyl enol ethers are less prone to hydrolysis. This is the reason why they are preferred over trimethyl silyl enol ethers for this reaction. A variety of triisopropyl silyl enol ethers are converted into α-azido ketones.



SCHEME - 12

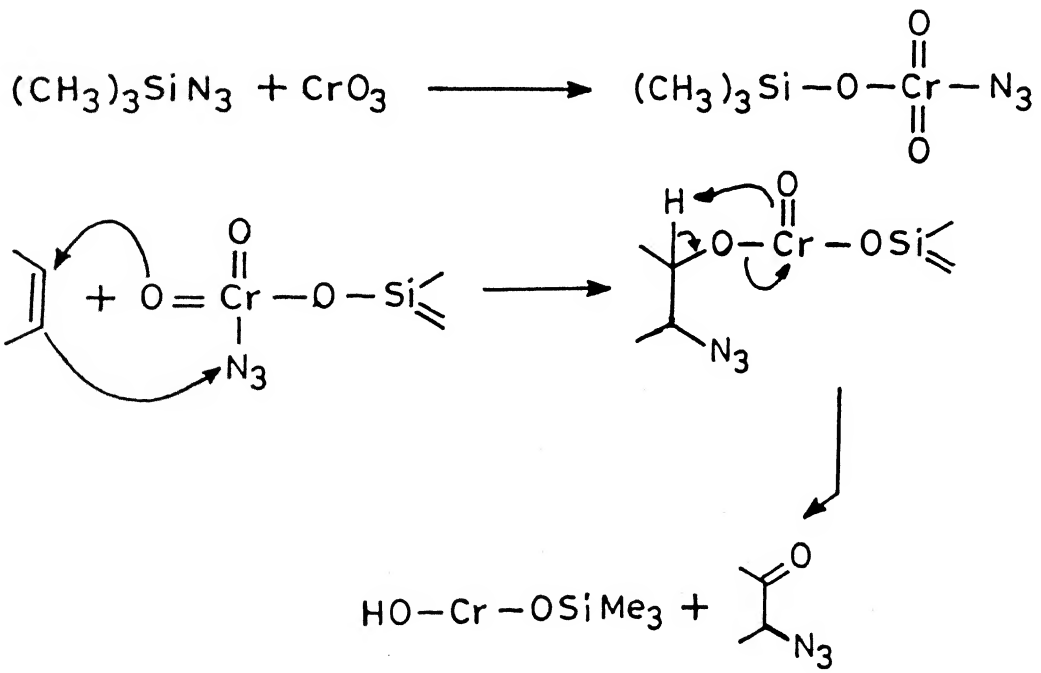
II.C.2 RESULTS AND DISCUSSION

In the introduction part of this chapter a brief literature survey pertaining to the synthesis of α-azido carbonyl compounds and their utility in organic synthesis has been described. Most of the methods for the preparation of α-azido carbonyl compounds rely upon halide displacement by azide anion[16], and it is possible that the chemistry of this class of compounds has not been fully explored because of the lack of suitable methods for their preparation. Few scattered reports[17-19] of their preparation from olefins using $PhI(OAc)_2$-$TMSN_3$ are described in the literature, however, these methods are not general in nature and 8-10 equivalents of the reagents are required for completion of the reaction. Keeping all these factors in mind, we wanted to develop a general method with the readily available starting materials and reagents. Our attention was drawn towards a recent report[21] where a combination of $TMSN_3$-CrO_3 has been used in converting aldehydes into the corresponding acyl azides. The mechanism proposed by the authors of this work is as shown below :



We, however, presumed that since chromyl chloride CrO_2Cl_2 is known to convert olefins into α-chloro ketones (or chlorohydrins) and if the above combination of CrO_3-$TMSN_3$ gives a species similar to chromyl azide, it is possible to convert olefins into α-azido carbonyl compounds. Indeed we found that a combination of mole equivalents of $TMSN_3$ and CrO_3 upon treatment with a variety of olefins produces good yields of the corresponding α-azido ketones. It is presumed that when CrO_3 is added to $TMSN_3$ in 1:1 ratio, a species such as $[(CH_3)_3SiOCrO_2N_3]$ is formed which is responsible for the product formation.

A tentative mechanism may be proposed as follows :



In order to find out if the reaction has wide acceptability and applicability, a variety of olefins were reacted and in all the cases the reaction proceeded smoothly to give the products.

In the cyclic case, four olefins have been studied. Thus cyclohexene 57 gave α-azido cyclohexanone 66 in 58% yield. Its IR spectrum showed peaks at 2100 cm^{-1} corresponding to $-N_3$ group and 1710 cm^{-1} corresponding to the $\rangle C = O$ group. In its ^1H NMR spectrum, peaks at δ 1.1-1.9 (m, 4H, $2X-CH_2-$), 2.17-2.28 (m, 2H, $-CH_2-\underset{|}{C}HN_3$), 2.46-2.68 (m, 2H, $-CH_2-\overset{O}{\overset{\|}{C}}-$), 3.80-4.10 (m, 1H, $\rangle CH-N_3$) were observed, thus confirming its structure. Cyclododecene 59 gave α-azido cyclododecanone 68 in 82% yield. There was no indication for the formation of any other product. Its IR spectrum showed peaks at 2100 cm^{-1}, 1710 cm^{-1} for $-N_3$ and $\rangle C = O$ groups respectively. ^1H NMR spectrum showed signals at δ 1.0-2.17 (m, 18H, $9X-CH_2-$), 2.34-2.70 (t, 2H, $-CH_2-\overset{O}{\overset{\|}{C}}-$), 3.85-4.17 (t, 1H, $-\underset{|}{C}H-N_3$). Likewise, cyclopentene 56 and cycloheptene 58 also gave the corresponding α-azido ketones 65 and 67 respectively which have been thoroughly characterised by ^1H NMR and IR spectroscopy.

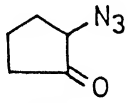
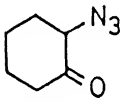
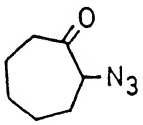
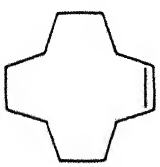
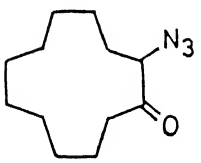
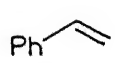
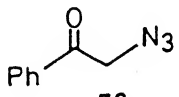
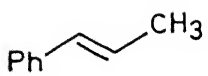
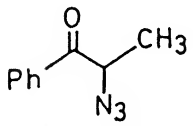
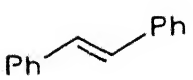
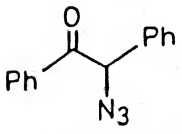
After successfully applying this reagent system to cyclic olefins we diverted our attention on to acyclic olefins. When 1-tridecene 60 was treated with this reagent system, 1-azido-2-tridecanone 69 was formed in 78% yield. In this case addition took place in Markownikoff fashion leading to the formation of only one regioisomer. In the IR spectrum, 69 showed peaks at 1720 and 2100 cm^{-1} corresponding to $\rangle C = O$ and $-N_3$ groups respectively. Its ^1H NMR spectrum showed signals at δ 0.7-1.7 (m, 21H, $-CH_3$, $9X-CH_2-$), 2.2-2.7 (m, 2H, $-CH_2-\underset{|}{C}=O$), 3.7- 4.08 (s, 2H, $-\underset{|}{\overset{O}{\overset{\|}{C}}}-CH_2-N_3$). On the other hand, cis-2-octene 61 gave a regioisomeric mixture of two compounds 2-azido-3-octanone 70 and 3-azido-2-octanone 71 in 62% and 38% ratio in a overall yield of 51%. Both these compounds had very close R_f value and hence could

not be separated by chromatography. Their ratio was, however, found out from ^1H NMR spectral analysis. The compound showed peaks at 1720 and 2100 cm^{-1} corresponding to $\rangle C = O$ and $-N_3$ respectively in its IR spectrum. ^1H NMR spectrum had signals at δ 0.7-1.7 (m, 11H CH_3, 4x-CH_2-), 2.18 (s, 3H, $-\overset{O}{\overset{|}{C}}-CH_3$), 2.4-2.68 (t, 2H, $-CH_2-\overset{O}{\overset{|}{C}}-$), 3.68-4.08 (m, 1H, $-\overset{|}{C}HN_3$).

Phenyl substituted olefins also gave the desired α-azido ketones without any cleavage of the C-C bond. Thus, styrene 62 gave phenacyl azide 72 in 70% yield. Its IR spectrum showed peaks at 1690 and 2100 cm^{-1} corresponding to $\rangle C = O$ and $-N_3$ groups respectively and ^1H NMR spectrum showed signals at δ 4.4-4.6 (s, 2H, $-\overset{O}{\overset{\|}{C}}-CH_2-N_3$), 7.34-7.8 (m, 3H, aromatic), 8.0-8.34 (m, 2H, aromatic). β-Methyl styrene 63 gave α-azido propiophenone 73 in 60% yield. Trans-stilbene 64 gave 1-azido-1,2-diphenyl ethanone 74 in 76% yield. These compounds were thoroughly characterised by their spectral data. Surprisingly, in the case of trans-stilbene, a small amount (8%) of benzaldehyde was formed due to C-C bond cleavage.

The results obtained in the present study clearly indicate that the present reagent system is a simple alternative to the other existing reagents for this conversion of olefins to α-azido ketones.

TABLE 1

S.No.	Olefin	Product	Time	Yield %
1	56	 65	24	69
2	57	 66	24	58
3	58	 67	24	76
4	 59	 68	24	82
5	$CH_3(CH_2)_{10}CH=CH_2$ 60	$CH_3(CH_2)_{10}-\overset{O}{\overset{\|}{C}}-CH_2-N_3$ 69	24	78
6	$CH_3(CH_2)_4CH=CHCH_3$ 61	$CH_3(CH_2)_4\overset{O}{\overset{\|}{C}}-\overset{N_3}{\overset{\|}{CH}}-CH_3$ 70 + $CH_3(CH_2)_4\overset{N_3}{\overset{\|}{CH}}-\overset{O}{\overset{\|}{C}}-CH_3$ 71	24	51
7	 62	 72	10	70
8	 63	 73	10	60
9	 64	 74	10	76

II.C.3 EXPERIMENTAL

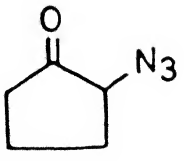
General

Azidotrimethylsilane was obtained from Aldrich Chemical Company and was used as received. Other solvents and reagents were purified according to the procedure followed in Section I.A.3.

General procedure for the one step conversion of olefins to α-azido ketones

To a solution of azidotrimethylsilane (174 mg, 1.5 mmol) in 2 ml of dry CH_2Cl_2 was added CrO_3 (150 mg, 1.5 mmol) and the reaction mixture was stirred for 15 min at 10°C during which all the CrO_3 gradually dissolved. To this reaction mixture was added a solution of 1 mmol of the olefin dissolved in 2 ml of dry CH_2Cl_2 dropwise at 10°C and stirring was continued at RT for the time mentioned in Table-1. The reaction mixture was filtered through a pad of celite and the pad was thoroughly washed with CH_2Cl_2 (2x25 ml). The solvent was evaporated on the rotary evaporator and the crude product was purified by column chromatography [eluent : petroleum ether - ethyl acetate].

2-Azido cyclopentanone 65



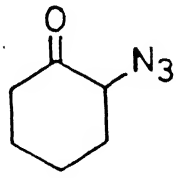
Yield : 69%

IR spectrum (neat) ν_{max} : 1690 (C=O), 2100 ($-N_3$) cm^{-1}.

^1H NMR spectrum (CCl_4) : δ 1.1-2.1 (4H, m, 2X-CH_2-), 2.53 (2H, m,

$-\underline{CH_2}-\overset{|}{C}=O)$, 3.8-4.01 (1H, m, $-\underset{|}{CH}N_3$).

2-Azido cyclohexanone 66

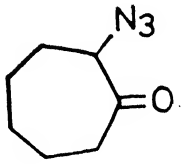


Yield : 58%

IR spectrum (neat) ν_{max} : 1710 (C=O), 2100 ($-N_3$) cm^{-1}.

^1H NMR spectrum (CCl_4) : δ 1.1-1.9 (4H, m, 2X-CH_2-), 2.17-2.28 (2H, m, $-\underline{CH_2}-\overset{|}{C}HN_3$), 2.46-2.68 (2H, m, $-CH_2-\overset{O}{\overset{\|}{C}}-$), 3.8-4.10 (1H, m, $\diagdown\!\!\diagup$ CH-N_3).

2-Azido cycloheptanone 67

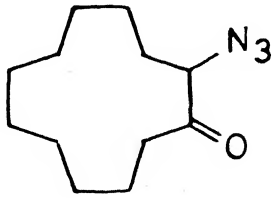


Yield : 76%

IR spectrum (neat) ν_{max} : 1710 (C=O), 2100 ($-N_3$) cm^{-1}.

^1H NMR spectrum ($CDCl_3$) : δ 1.1-2.17 (8H, m, 4X-CH_2-), 2.34-2.68 (2H, m, $-CH_2-\overset{O}{\overset{\|}{C}}-$), 3.9-4.17 (1H, m, $\diagdown\!\!\diagup$ CH-N_3).

2-Azido cyclododecanone 68



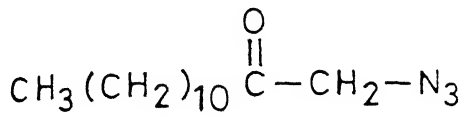
Yield : 82%

m.p. : 65°C

IR spectrum (CCl_4) ν_{max} : 1710 (C=O), 2100 ($-N_3$) cm^{-1}.

^1H NMR spectrum (CCl_4) : δ 1.0-2.17 (18H, m, 4X-CH_2-), 2.34-2.70 (2H, t, $-CH_2-\overset{O}{\overset{\|}{C}}-$), 3.85-4.17 (1H, t, $\rangle CH-N_3$).

1-Azido-2-tridecanone 69



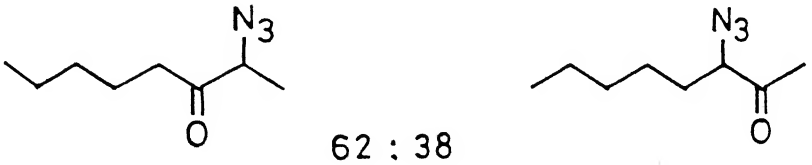
Yield : 78%

m.p. : 81°C

IR spectrum (CCl_4) ν_{max} : 1720 (C=O), 2100 ($-N_3$) cm^{-1}.

^1H NMR spectrum (CCl_4) : δ 0.7-1.7 (21H, m, $-CH_3$, 9X-CH_2-), 2.2-2.7 (2H, m, $-CH_2-\overset{O}{\overset{\|}{C}}-$), 3.7-4.08 (2H, s, $-\overset{O}{\overset{\|}{C}}-CH_2-N_3$).

Azido Ketones 70 and 71



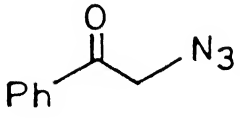
62 : 38

Yield : 51%

IR spectrum (neat) ν_{max} : 1720 (C=O), 2100 ($-N_3$) cm^{-1}.

^1H NMR spectrum (CCl_4) : δ 0.7-1.7 (11H, m, $-CH_3$, 4X-CH_2-), 2.18 (3H, s, $-CH_3$), 2.4-2.68 (2H, t, $-CH_2-\overset{O}{\overset{\|}{C}}-$), 3.68-4.08 (1H, m, 2X $\rangle CH-N_3$).

Phenacyl azide 72

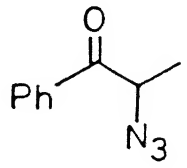


Yield : 70%

IR spectrum (neat) ν_{max} : 1690 (C=O), 2100 ($-N_3$) cm^{-1}.

^1H NMR spectrum (CCl_4) : δ 4.4-4.6 (2H, s, $-\overset{O}{\overset{\|}{C}}-CH_2-N_3$), 7.34-7.85 (3H, m, aromatic), 8.0-8.34 (2H, m, aromatic).

α-Azido propiophenone 73

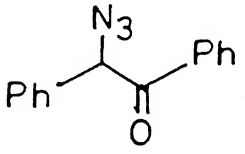


Yield : 60%

IR spectrum (neat) ν_{max} : 1685 (C=O), 2100 ($-N_3$) cm^{-1}.

^1H NMR spectrum (CCl_4) : δ 1.51-1.68 (3H, d, $-CH_3$), 4.34-4.8 (1H, q, $-\overset{O}{\overset{\|}{C}}-CH<$), 7.17-7.68 (3H, m, aromatic), 7.85-8.17 (2H, m, aromatic).

1-Azido-1,2-diphenyl ethanone 74



Yield : 76%

m.p. : 65°C

IR spectrum (CCl_4) ν_{max} : 1690 (C=O), 2100($-N_3$) cm^{-1}.

^1H NMR spectrum (CCl_4) : δ 5.68 (1H, s, Ph-$\underset{|}{CH}$-N_3), 7.17-7.85 (7H, m, aromatic), 7.9-8.34 (3H, m, aromatic).

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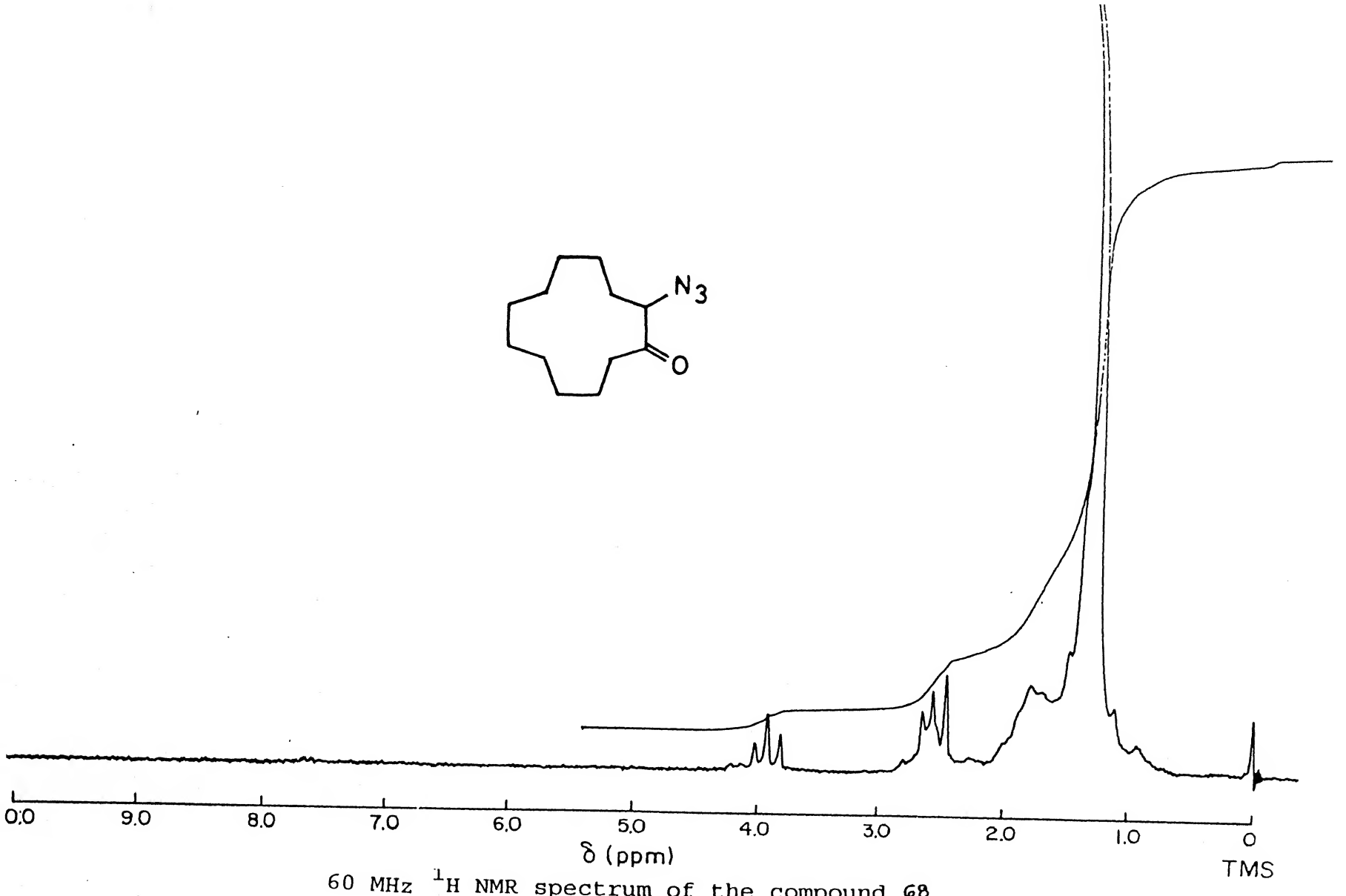
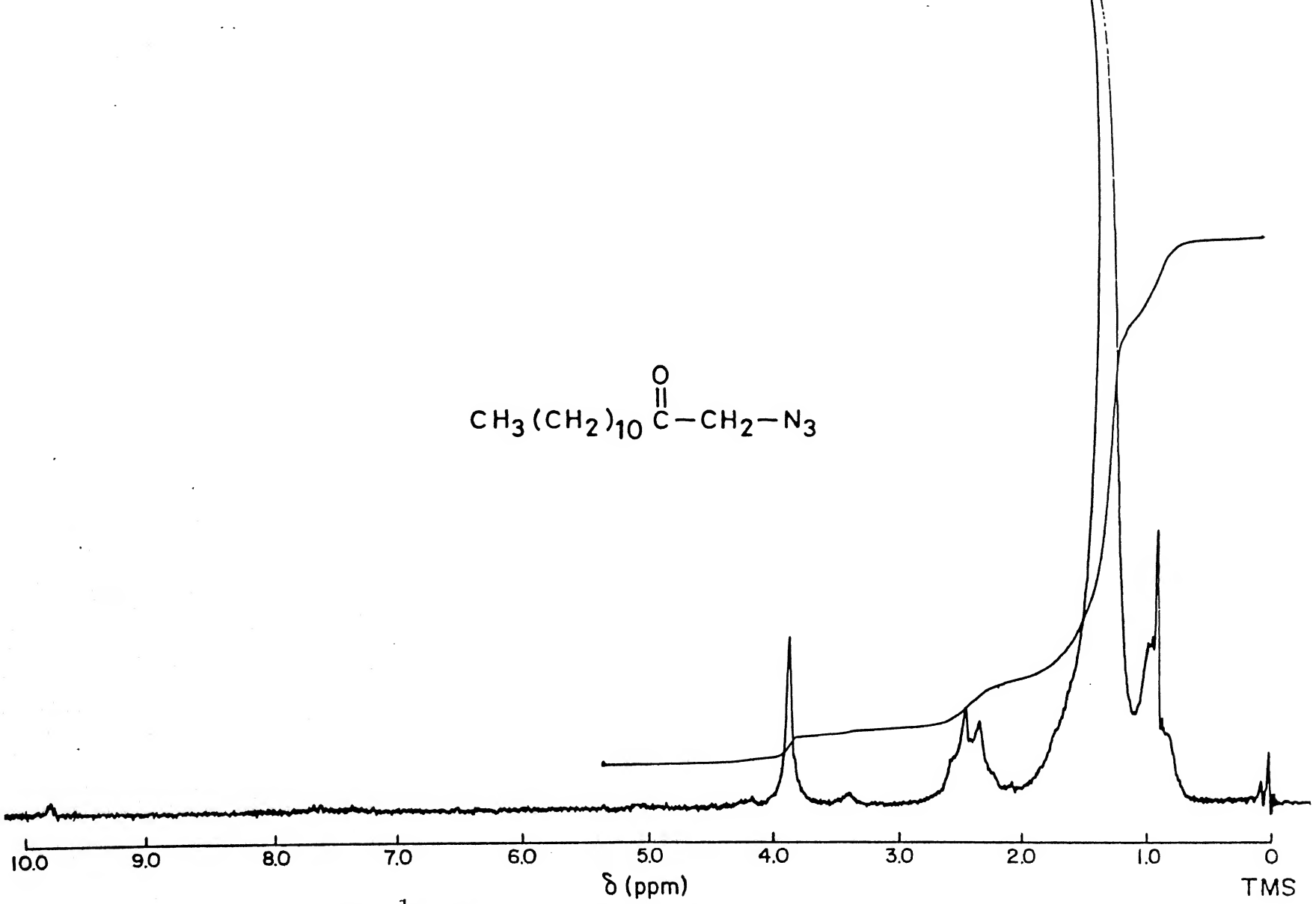
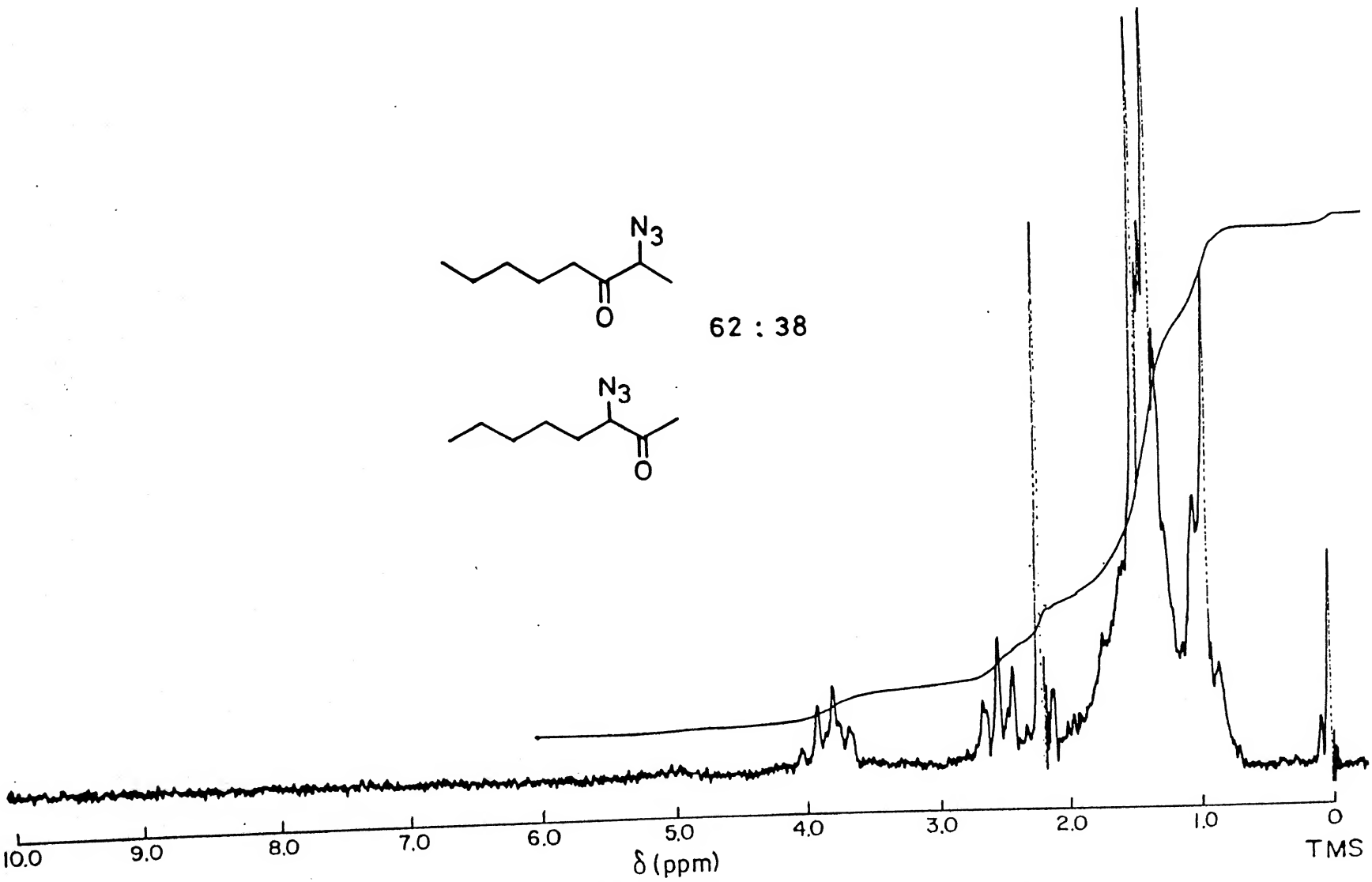


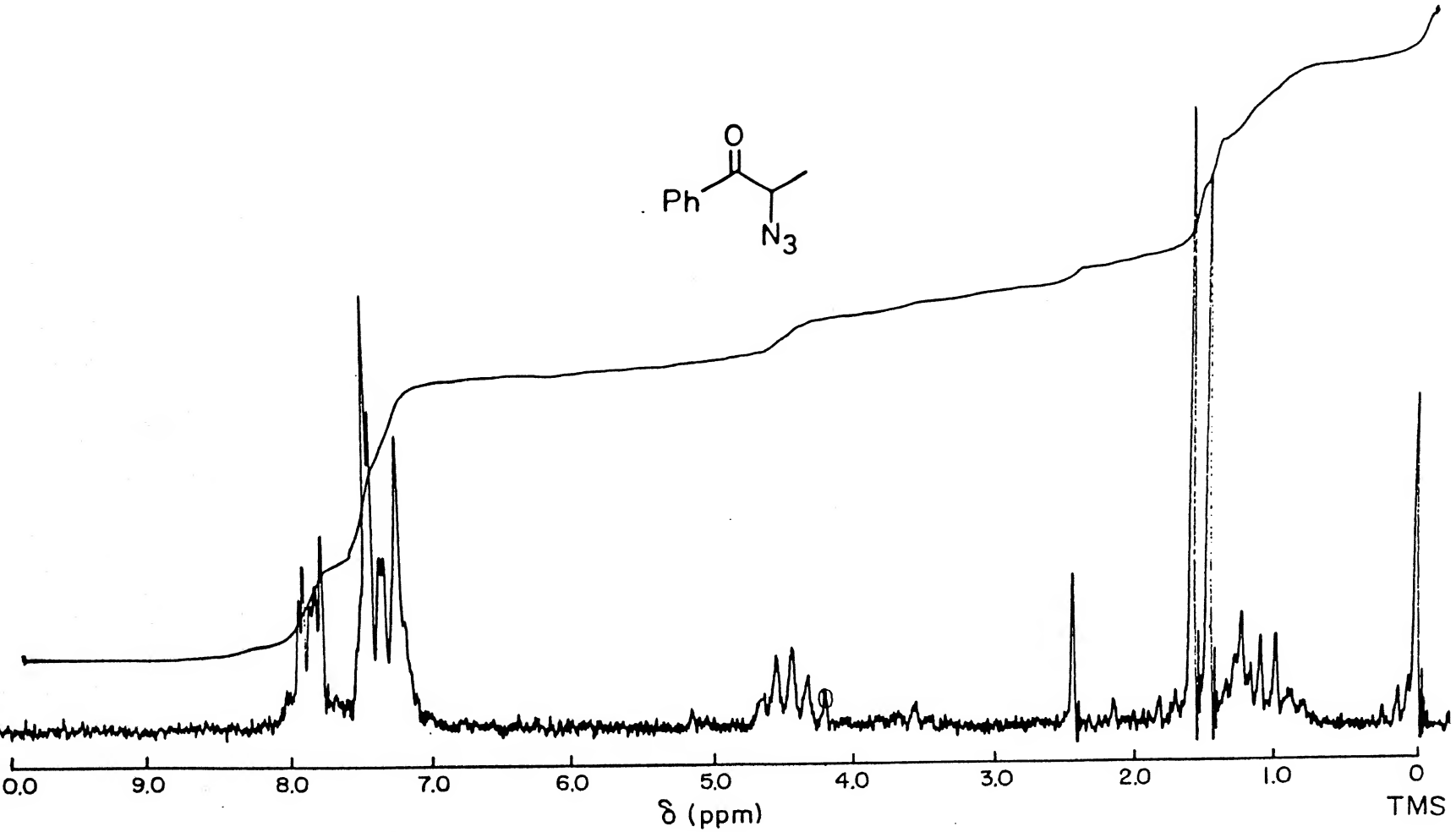
60 MHz ^{1}H NMR spectrum of the compound 68



60 MHz ^{1}H NMR spectrum of the compound 69



60 MHz ^{1}H NMR spectrum of the compound 70 and 71



60 MHz ^{1}H NMR spectrum of the compound 73

CHAPTER II

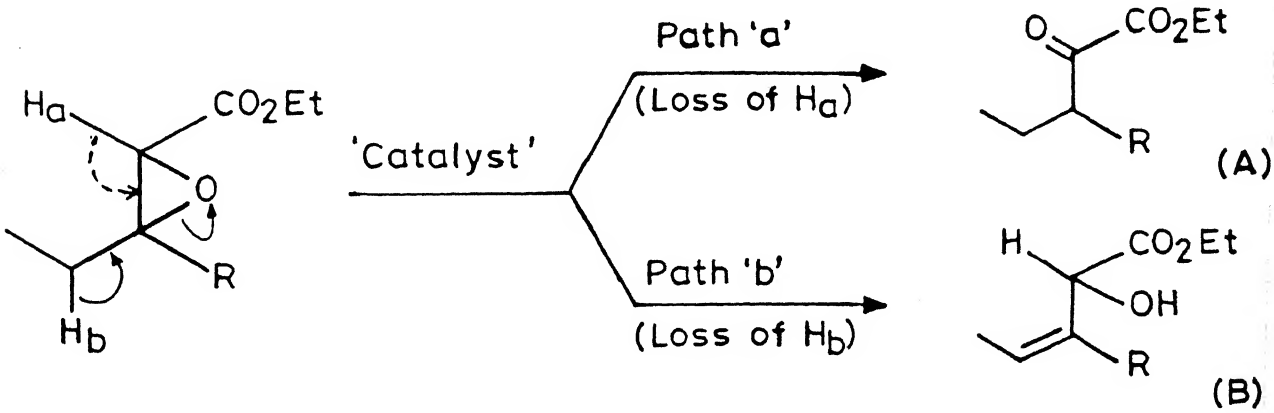
PART D

H-ZSM-5 CATALYSED REGIOSELECTIVE ISOMERISATION OF GLYCIDIC ESTERS TO α-HYDROXY-β,γ-UNSATURATED ESTERS

II.D.1 INTRODUCTION

Glycidic esters have an epoxy and an ester group in a relation which in compounds having two unsaturated groups is known as conjugated. This relation, doubtless, is responsible for the ease with which they can either be rearranged or reacted with a variety of reagents. Some of the reactions of glycidic esters are presented in the introduction part in brief.

Glycidic esters, depending on their structures and the catalyst employed, undergo mainly two types of isomerisation as indicated in Scheme 1.

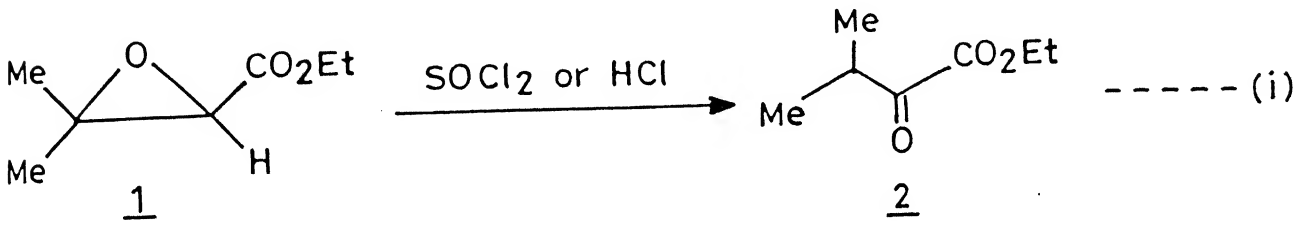


SCHEME - 1

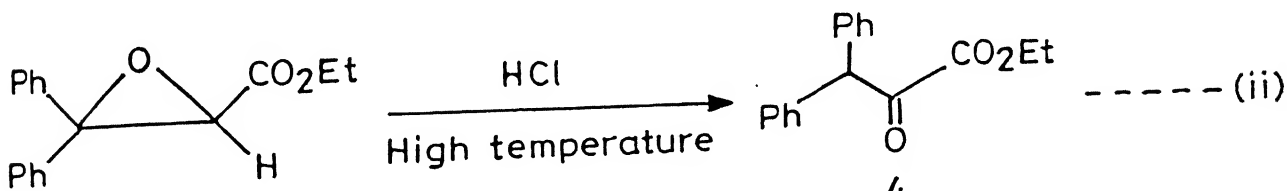
When a proton α to the ester moiety is lost the product formed is an α-keto ester (A). On the other hand, when H_b is lost α-hydroxy-β,γ-unsaturated ester (B) is formed. For example, when ethyl-3-methyl-2,3-epoxy butanoate 1 was reacted with acid catalysts such as $SOCl_2$ or HCl it was isomerised to ethyl dimethyl pyruvate 2[1] (equation (i), Scheme 2). For the conversion of ethyl-3,3-diphenyl glycidate 3 to ethyl diphenyl pyruvate 4

Bliche et al[2] had to use HCl gas at elevated temperatures (equation (ii), Scheme 2). In addition to these catalyst, BF_3 gas in benzene has been employed[3] for such isomerisations. (equation (iii), Scheme 2).

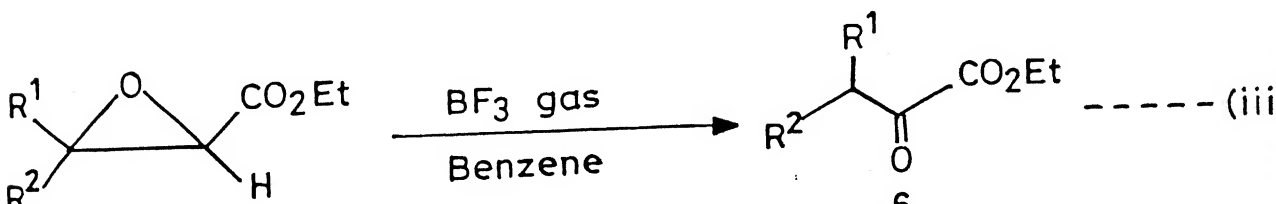
Apart from migration of hydrogen, migration of other groups such as carboethoxy leading to the formation of α-formyl esters (equation (iv), Scheme 2) has also been reported in the literature[4].



1 2 ----- (i)

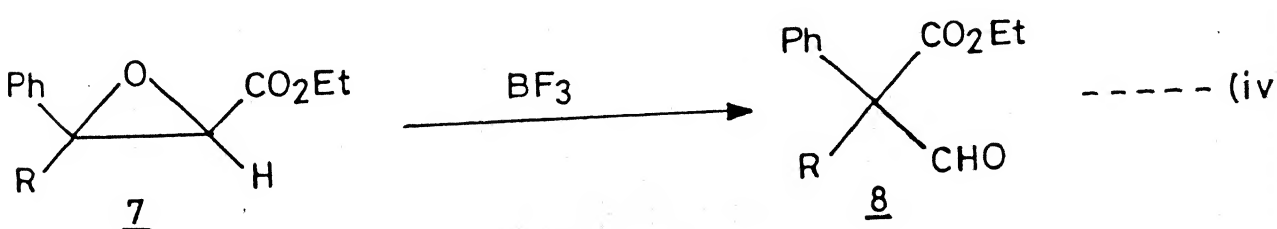


3 4 ----- (ii)



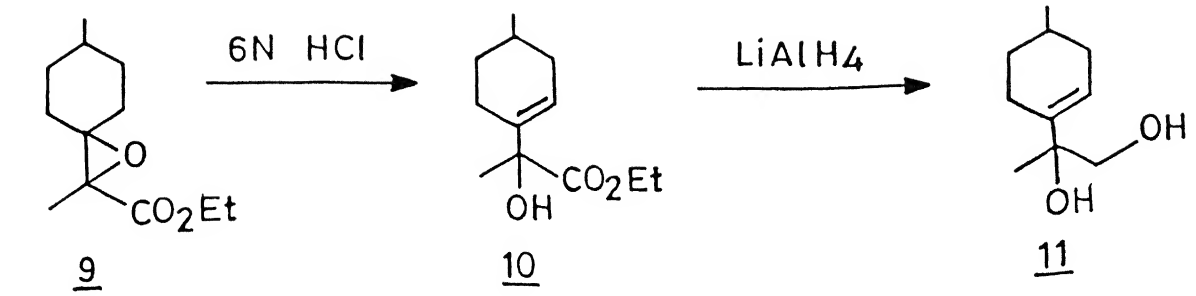
5 6 ----- (iii)

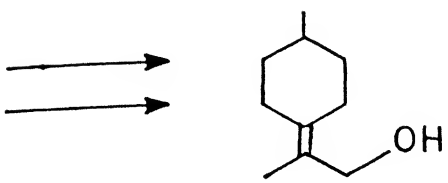
$R^1 = C_6H_5$; R^2 = H, alkyl



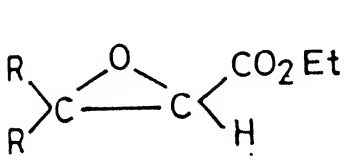
7 8 ----- (iv)

SCHEME-2





------ (i)



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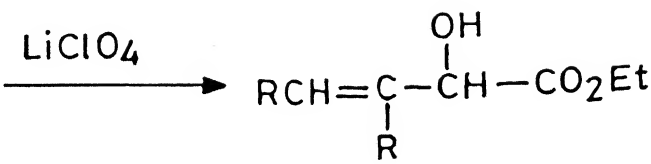

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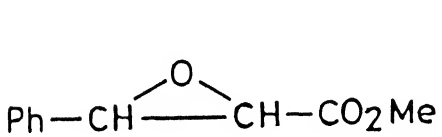
------ (ii)



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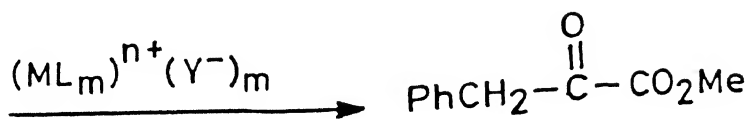

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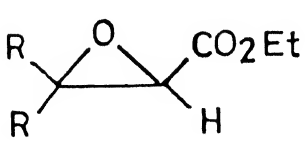

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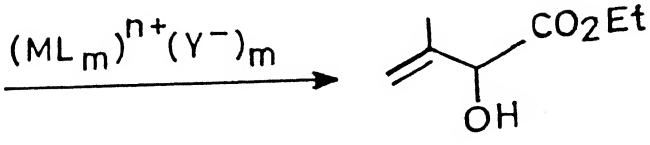

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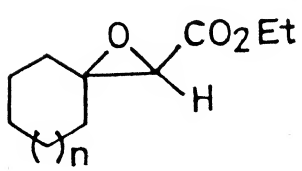
------ (ii



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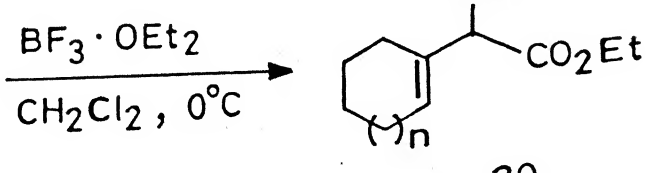

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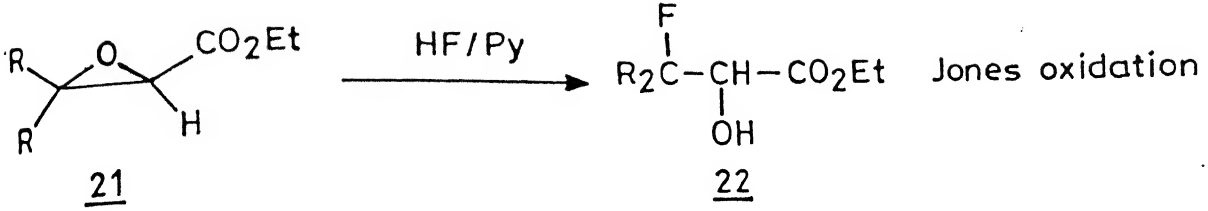
------ (i

SCHEME -3



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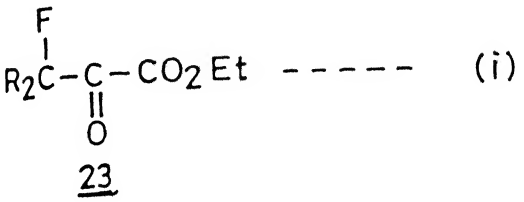

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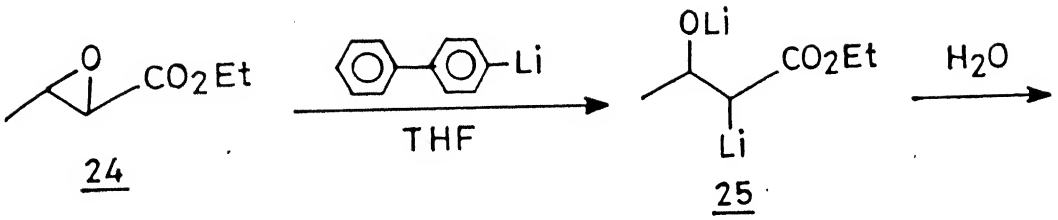
R = alkyl, aryl



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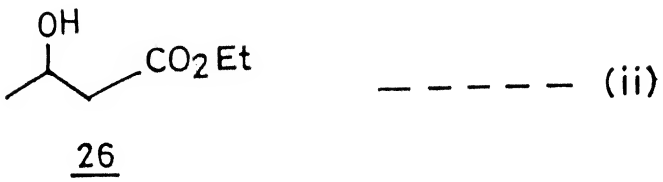

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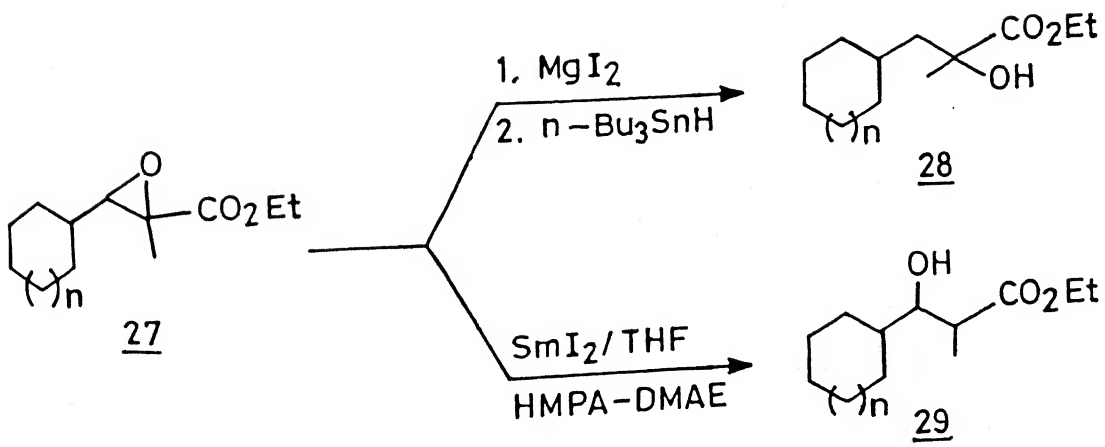


27 28 29

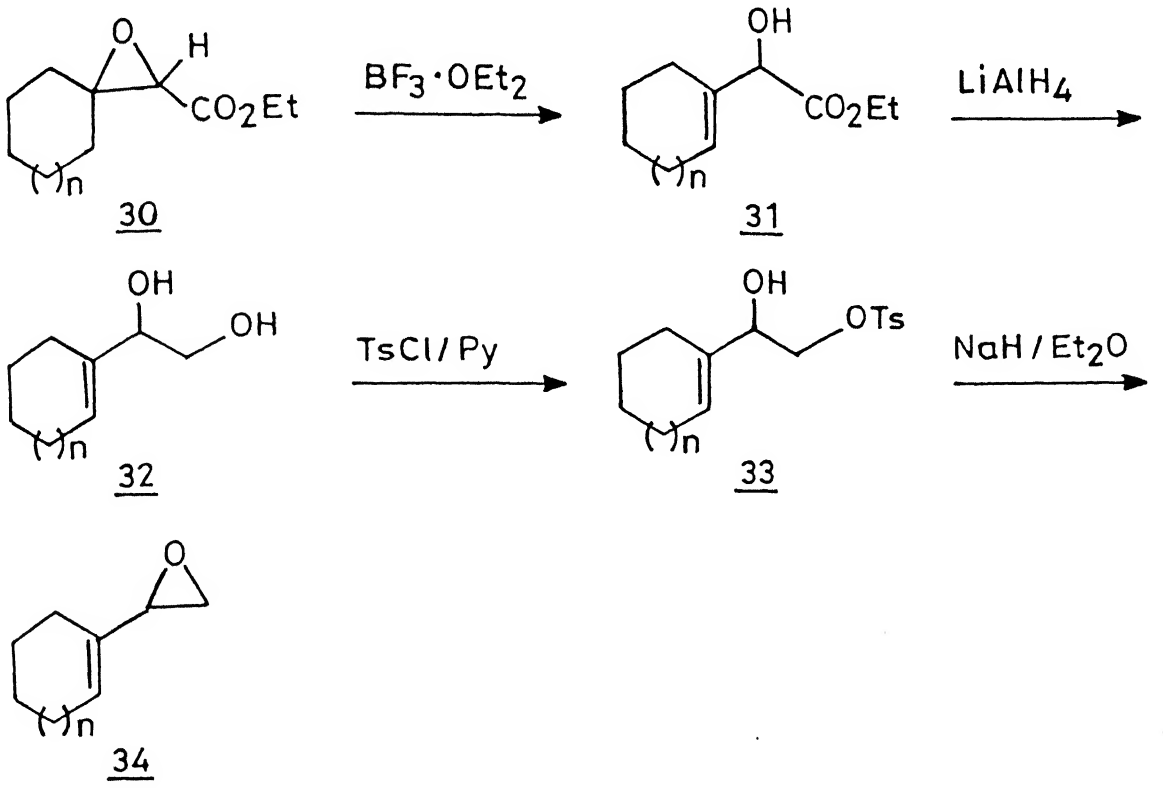
SCHEME -4

Apart from the above described isomerisation, glycidic esters have also been found to undergo many other reactions where the oxirane ring is regioselectively opened by nucleophiles to give products of diverse synthetic utility. Thus, for example, glycidic esters react with HF-Py to afford regioselective fluorohydrins, which are converted to the fluorinated pyruvates[9] (equation (i), Scheme 4).

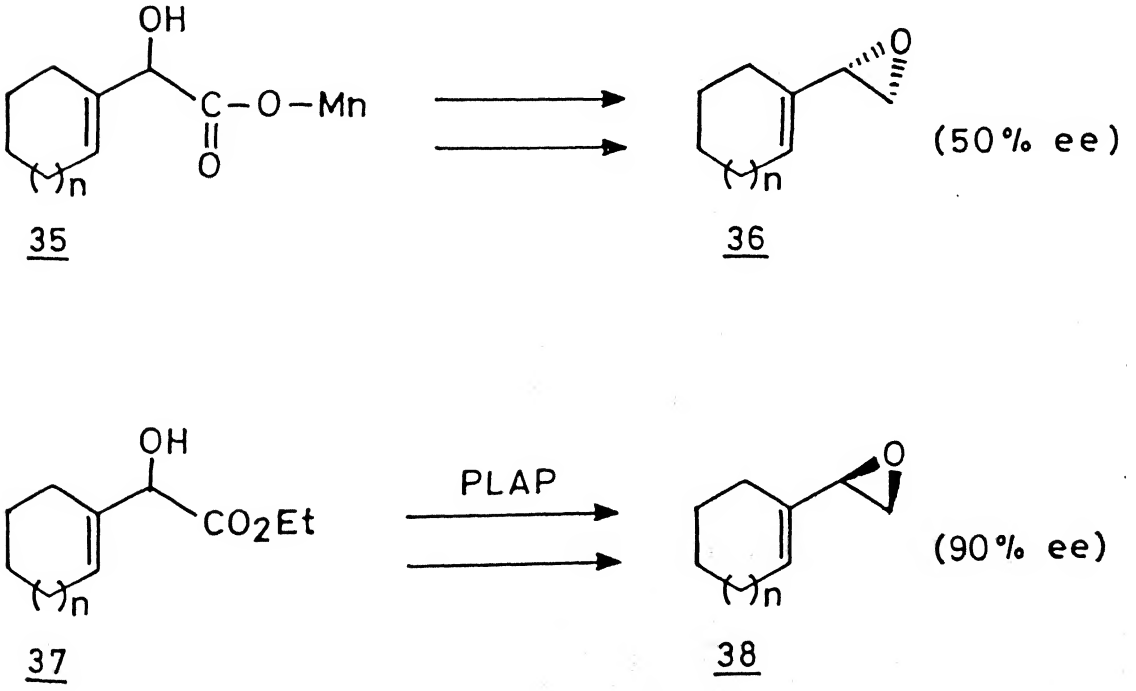
Regioselective reduction of glycidic esters with biphenyl lithium, biphenyl potassium, naphthyl magnesium or naphthyl lithium could be performed which leads to the C-O bond cleavage at their α-site to afford β-hydroxy esters with appreciable selectivity[10] (equation (ii), Scheme 4).

Recently, Otsubo et al[11] have reported new methods for the facile regioselective reduction of oxirane ring of glycidic esters. Thus, sequential treatement of a glycidic ester with MgI_2 and tributyltinhydride affords predominantly the α-hydroxy ester 28 (equation (iii), Scheme 4) with complete retention of configuration at the α carbon atom. On the other hand, SmI_2 in THF in the presence of HMPA and 2-dimethylaminoethanol (DMAE) reduces the glycidic esters to the β-hydroxy esters 29 with complimentary regioselectivity, again with retention of configuration at the β carbon atom[11].

From our group, a new synthesis of vinyl epoxides has been reported[12] from glycidic esters via α-hydroxy-β,γ-unsaturated esters (Scheme 5). Further, these vinyl epoxides have been synthesised in both the optically active forms 36 and 38 by using (-)-menthol as the chiral auxiliary and by resolution using pig liver acetone powder[13] respectively (Scheme 6).



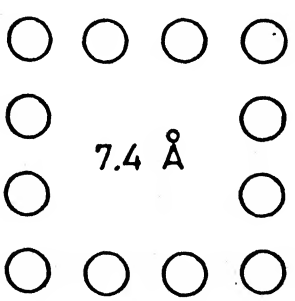
SCHEME-5



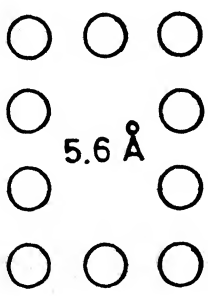
SCHEME-6

From the foregoing discussions about the reactions of glycidic esters it is clear that they are important intermediates in organic synthesis. Particularly, as vinyl epoxide is an important functionality in organic synthesis, the above described (cf. Schemes 5 and 6) synthesis is of special significance. This, of course, involves isomerisation of glycidic esters into α-hydroxy-β,γ-unsaturated esters as the first key step. Although the method discovered for such isomerisation in our laboratory is mild and high yielding (cf. Ref. 12), it was occasionally found that variation in the concentration of the acid catalyst or in the reaction temperature led to the decreased yields of the isomerised product. As a result of this we were on the look out for an alternate catalyst for such a transformation. For the past two decades zeolite catalysis has gained a lot of importance because of its mild reaction conditions, ease of workup, high selectivities and catalyst recoverability[14].

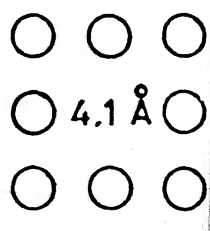
Zeolites are crystalline aluminosilicates with a highly ordered crystalline structure. Cavities of definite size are found in the rigid three dimensional network composed of SiO_4 and AlO_4 tetrahedron. Depending on the type of zeolite, distinction has been made and the zeolites are categorised into three categories : (i) large, (ii) medium and (iii) small[15].



12 ring
Large



10 ring
Medium



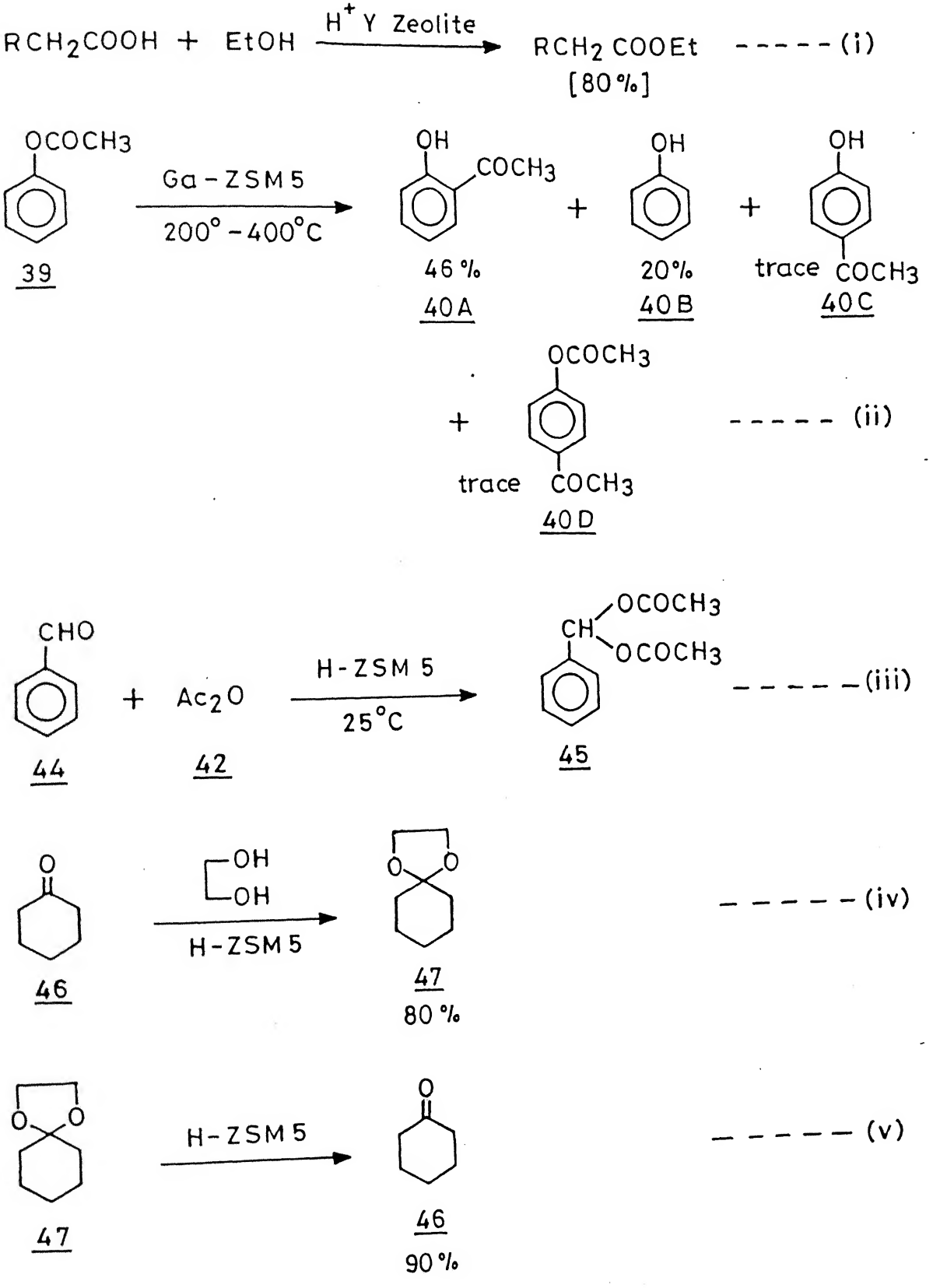
8 ring
Small

Some of the important representative examples of zeolites are mentioned below :

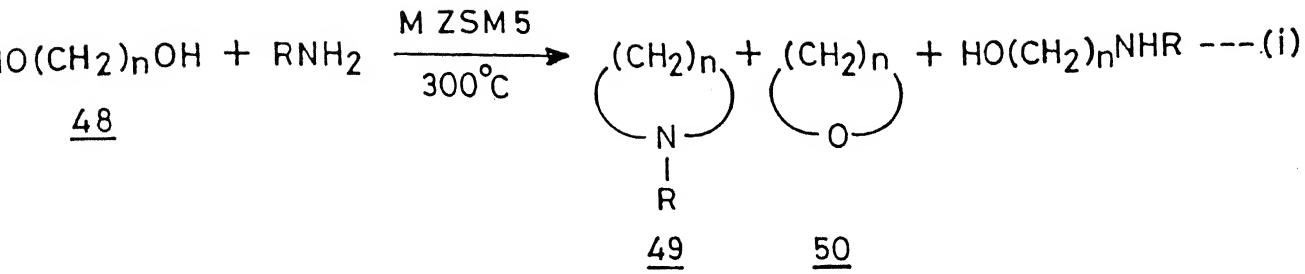
Small	Medium	Large
Erionite	ZSM-5	Fauzisite
Chabazite	ZSM-11	X/Y zeolite
	ZSM-22	Mordenite
	TS-1	ZSM-4
	TS-2	ZSM-12
	Silicalite	

The most important application of zeolites is in reactions which are catalyzed by proton acids and Lewis acids. Here the change from homogeneous to heterogeneous procedure brings advantage in respect of easy separation, disposal of the catalyst and avoidance of corrosion etc. In this regard, their shape selectivity has an added advantage on the composition of the product and on the preferred selectivity for the p-isomer in isomerisation of aromatic compounds. The thermal stability of zeolites permits[16] them to be used at high (> 150^{o}C) temperatures also, provided that the organic compounds to be reacted do not decompose at this temperature. Due to the above mentioned advantages, there has been a sudden surge of activity in the recent past to bring about a number of useful functional group transformations in organic synthesis using zeolite catalysts. A few representative examples are given below :

(i) When acids are heated in the presence of HY zeolites and ethanol, the corresponding esters are formed[17] in excellent yields (equation (i), Scheme 7).


RCH2COOH + EtOH
H+ Y Zeolite
RCH2 COOEt
[80 %]
(i)
OCOCH3
39
Ga - ZSM 5
200° - 400°C
OH
COCH3
46 %
40A
OH
20%
40B
OH
trace
COCH3
40C
(ii)
OCOCH3
trace
COCH3
40D
CHO
44
Ac2O
42
H-ZSM 5
25°C
CH
OCOCH3
OCOCH3
45
(iii)
O
46
OH
OH
H-ZSM5
47
80 %
(iv)
H-ZSM5
46
90 %
(v)

SCHEME-7

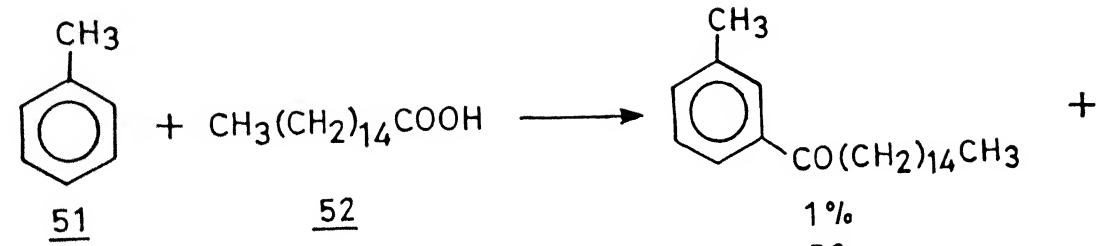


48 49 50

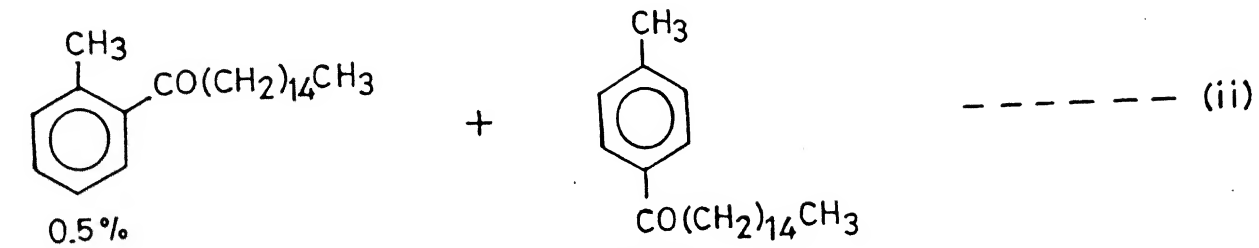
n = 4 or 5

R = CH_3 or CH_2CH_3

M = Cr, V, Mn, Mo, etc



51 52 1% 53



0.5% 54 98.5% 55

SCHEME-8

(ii) Ga-ZSM-5[18] is used in converting phenyl acetates into 2-hydroxyacetophenone in a manner analogous to the Fries rearrangement (equation (ii), Scheme 7).

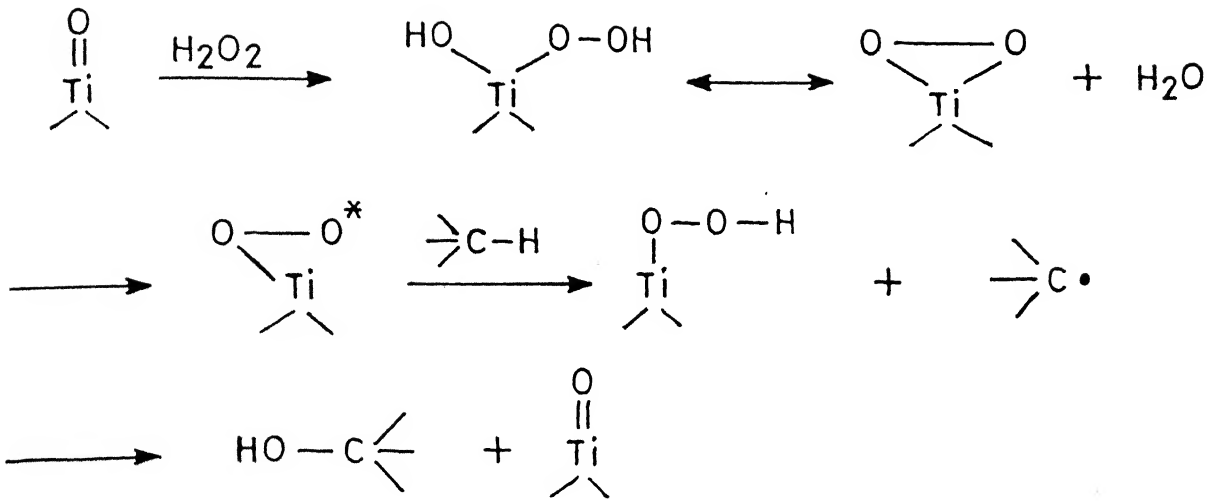
(iii) Aldehydes are transformed into 1,1-diacetates when catalyzed by H-ZSM-5[19] (equation (iii), Scheme 7).

(iv) Interestingly, H-ZSM-5 has been utilized both in the formation of acetals[20] as well as for the cleavage of acetals[21] (cf. equations (iv) and (v), Scheme 7).

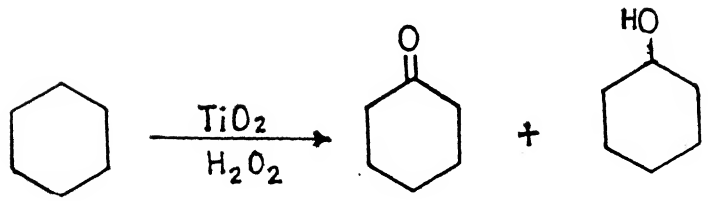
(v) Synthesis of 5- and 6-membered heterocycles has been demonstrated recently by Subba Rao et al[22] using chromium modified ZSM-5 zeolite catalyst (equation (i), Scheme 8).

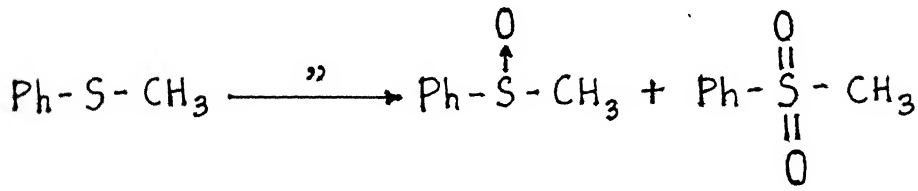
(vi) Likewise, faujasite type zeolites $Na_{56}(AlO_2)_{56}(SiO_2)_{136}$ have been modified with Ce^{3+} and used efficiently for the Friedel-Crafts acylation of toluene and p-xylene in a highly selective manner[23] (equation (ii), Scheme 8).

Apart from the above mentioned reactions, titanium and vanadium silicates upon combination with H_2O_2 have been reported to form peroxy radicals (Scheme 9) which are powerful oxidising agents[24]. They have been used in a few interesting transformations (Scheme 10).



SCHEME - 9





SCHEME 10

II.D.2 RESULTS AND DISCUSSION

In the introduction part of this chapter, literature details regarding the reactions of glycidic esters have been described. As is also described that from our laboratory recently it has been reported that $ClSiMe_3$ or $BF_3.Et_2O$ can bring about facile regioselective isomerisation of glycidic esters into α-hydroxy-β, γ-unsaturated esters. The utility of these compounds has also been well realized in our laboratory as the latter compounds have been converted into achiral and chiral vinyl expoxides. Further, their oxidation products are also very good Michael acceptors and powerful Diels-Alder heterodienes.

Because of the importance associated with the α-hydroxy-β.γ-unsaturated esters we were intertested in improving our earlier method of isomerisation of glycidic esters with $BF_3.Et_2O$ or $ClSiMe_3$. Towards the end of the introduction part of this chapter, a brief report on the application of zeolite catalysts has been delineated. The most important application of zeolites is in reactions catalyzed by proton acids and Lewis acids, where the change from homogeneous to heterogeneous procedure brings advantage with respect to easy separation, disposal of the catalyst and avoidance of corrosion etc. In this regard, their shape selectivity has an added advantage on the composition of the product. The thermal stability of zeolites permits them to be used at high temperatures. They are, therefore, advantageous for reactions in which the thermodynamic equilibrium requires high temperature. Further, catalytic recyclability and environmental pollution free properties makes them to be more attractive than

the conventional methods.

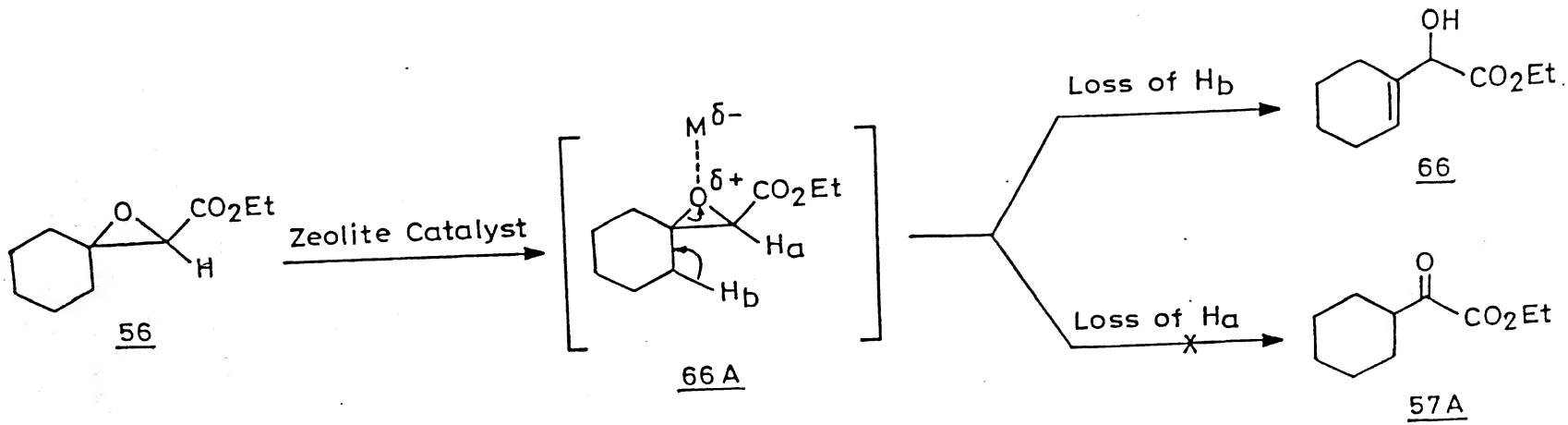
For the present study we, therefore, proposed to find if zeolites could bring about isomerisation of glycidic esters and if so whether they would show any regiochemical preference as zeolites depending upon their pore size and nature are highly shape selective. Indeed we have found that a glycidic ester upon heating with weight equivalent of H-ZSM-5 in refluxing benzene (or dichloroethane) is isomerised to α-hydroxy-β,γ-unsaturated ester. Formation of even trace amount of keto esters was not detected.

It is presumed that initially epoxy oxygen complexes with the zeolite leading to the formation of an intermediate 66A. Since the generation of a positive charge adjacent to an electron withdrawing carboethoxy group is not favourable, cleavage of C-O bond α to -COOEt group is prevented. Therefore, the intermediate 66A (cf. Scheme 11) may lose H_a or H_b to form 66 or 57A respectively. However, since 57A is not at all obtained in the present case the loss of H_a does not take place.

Other solvents like CCl_4 and CH_3CN were also inspected for these reactions. Although the reaction was clean in CCl_4 but in the case of acetonitrile only a trace amount of the product formation took place.

In order to access the generality of this zeolite mediated isomerisation a number of glycidic esters (cf. Table 1) were reacted. In all the cases, isomerisation took place quite smoothly and the results are summarized in Table 2.

Cyclohexanone glycidic ester 56 upon isomerisation gave



M : Zeolite Catalyst

SCHEME -11

ethyl-2-hydroxy-2-(1-cyclohexenyl) acetate 66 in 74% yield. It exhibited IR absorption at 3480 and 1730 cm^{-1} corresponding to -OH and C=O groups respectively. Its ^1H NMR spectrum showed signals at δ 5.83 (1H, br s, =CH-), 4.6-4.1 (3H, m, containing the ester quartet, J = 7 Hz, $-OC\underline{H}_2CH_3$ and $-C\underline{H}OH$), 3.1 (1H, br s, -OH), 2.4-1.97 (4H, m, allylic methylenes), 1.9-1.5 (4H, m, 2X-CH_2-) and 1.3 (3H, t, $-OCH_2C\underline{H}_3$, J = 7 Hz). The acetylated product of 66 exhibited IR bands at 1750-1740 cm^{-1} for $-O-\overset{\overset{O}{\|}}{C}-CH_3$ and $-\overset{\overset{O}{\|}}{C}-OCH_2CH_3$ groups. Its ^1H NMR spectrum showed peaks at δ 5.87 (1H, br s, =CH-), 5.17 (1H, s, $-C\underline{H}OAc$), 4.2 (2H, q, $-OC\underline{H}_2CH_3$, J = 7 Hz), 2.47-1.9 (7H, br s, CH_3-C=O and allylic methylenes), 1.83-1.53 (4H, br s, 2X-CH_2-) and 1.27 (3H, t, $-OCH_2C\underline{H}_3$, J = 7 Hz).

Likewise cyclopentanone and cycloheptanone glycidic esters 57 and 58 underwent smooth isomerisation and gave the corresponding α-hydroxy-β,γ-unsaturated esters 67 and 68 in 73% and 81% yields respectively. These products have been thoroughly characterised by their IR and ^1H NMR spectral data. Glycidic ester of 2-methyl cyclohexanone viz. 60 apparently gave an anamolous observation. The isomerised product 70 was found to contain the double bond at the less substituted carbon atom as was evident from its ^1H NMR spectrum which showed a broad singlet at δ 5.73 accounting for one proton and a doublet at δ 0.97 accounting for three protons with J = 6 Hz. The zeolite pore size and transition state shape selectivity are mainly responsible for the formation of this kinetically controlled product which had a double bond at the less substituted carbon atom. But interestingly when 65 was subjected to isomerisation, it gave the α-hydroxy-β,γ-unsaturated ester 75

in 32% yield. The IR spectrum of 75 showed bands at 3500 and 1730 cm^{-1} corresponding to -OH and ester C=O groups respectively. The β,γ-double bond in 75 was found to be at the more substituted carbon atom i.e., between C_1 and C_9 of the decalin system. This is apparent from the absence of a proton signal in the olefinic region of its ^1H NMR spectrum. The ^1H NMR spectrum showed signals at δ 4.6-4.1 (3H, m, -CHOH, containing the $-OC\underline{H}_2CH_3$ quartet, J = 7 Hz), 2.83 (1H, br s, -OH), 2.5-1.2 (18H, m, -CH, 7X-CH_2- containing the $-OCH_2C\underline{H}_3$ triplet, J = 7 Hz). Mass spectrum showed m/z 238 (M^+). Similarly, 3-acyclic systems were studied and the reactions took place smoothly in these cases also. For example, the glycidic ester 62 derived from acetone underwent isomerisation to yield the isomerised product 72 in 58% yield. The IR spectrum of the product showed peaks at 3460 and 1730 cm^{-1} corresponding to -OH and ester C=O groups respectively. Its ^1H NMR spectrum showed signals at δ 5.2-4.7 (2H, m, =CH-), 4.5 (1H, s, -C<u>H</u>OH), 4.13 (2H, q, $-OC\underline{H}_2CH_3$, J = 7 Hz), 3.18 (1H, br s, -OH), 1.63 (3H, m, $=C(CH_3)$-CH-), 1.25 (3H, t, $-OCH_2C\underline{H}_3$). Its mass spectrum showed m/z 145 $(M+1)^+$, 71 (M^+-COOEt). Likewise, glycidic ester 63 derived from 3-pentanone gave 73 in 66% yield which showed IR absorption at 3500 and 1715 cm^{-1} corresponding to -OH and ester C=O groups respectively. Its ^1H NMR spectrum showed signals at δ 5.35 (1H, br q, =CH-, J = 5.7 Hz), 4.82 and 4.28 (1H, br singlets, relative area ca 2.1, -CHOH), 4.03 (2H, q, $-OC\underline{H}_2CH_3$, J = 7 Hz), 3.33 (1H, br d, -OH), 1.92 (2H, t, $CH_3C\underline{H}_2$-C=CH, J = 7 Hz), 1.59 and 1.53 (3H, 2d, relative areas ca 2:1, CH_3-C=), 1.20 (3H, t, $C\underline{H}_3CH_2$-C=CH, J = 7 Hz), 0.90 (3H, t, $-OCH_2C\underline{H}_3$, J = 7 Hz). In a similar manner, the glycidic ester of acetophenone yielded the

corresponding isomerised product in 74% yield.

It is therefore expected that the present study of isomerisation of glycidic esters to α-hydroxy-β,γ-unsaturated esters using H-ZSM-5 should find application in organic synthesis. It is hoped that because of the aforementioned benefits associated with the use of zeolites, this isomerisation is industrially useful too.

TABLE 1

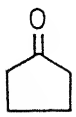
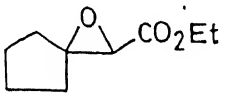
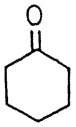
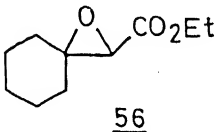
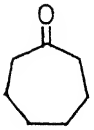
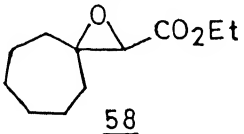
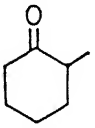
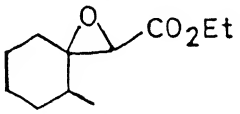
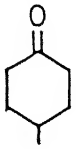
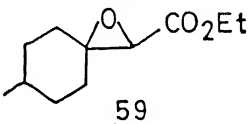
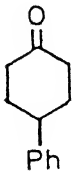
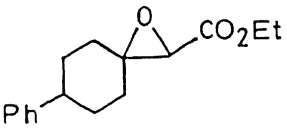
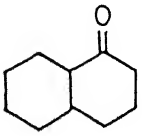
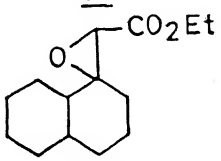
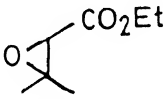
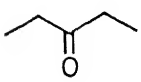
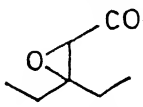
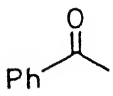
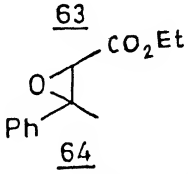
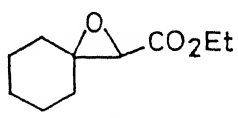
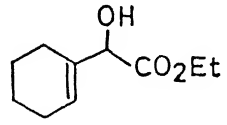
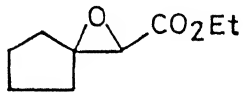
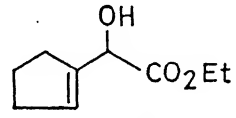
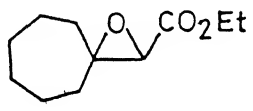
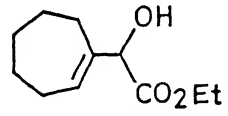
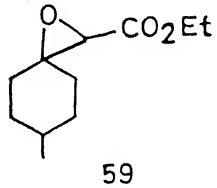
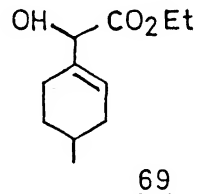
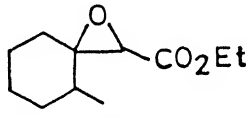
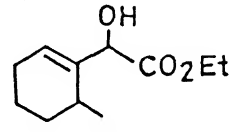
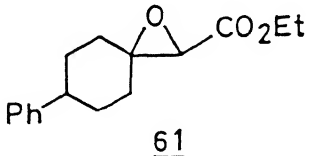
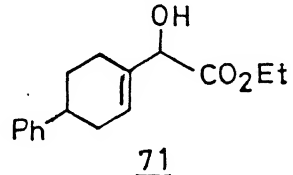
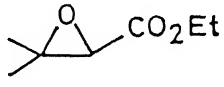
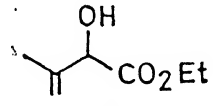
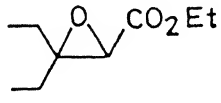
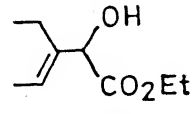
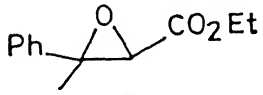
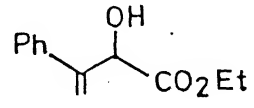
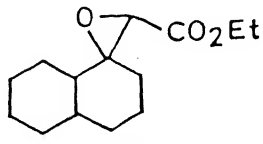
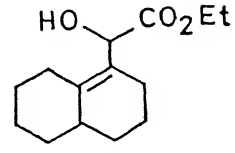
S. No	Ketone	Glycidicester	Time (hr)	Yield (%)
1		 57	4	37
2		 56	4	54
3		 58	4	40
4		 60	4	38
5		 59	4	67
6		 61	8	56
7		 65	8	46
8		 62	4	55
9		 63	4	56
10		 64	6	70

Table 2

Entry	Substrate	Product	Time (hr)	Yield (%)
1	 56	 66	1	74
2	 57	 67	1	73
3	 58	 68	1	81
4	 59	 69	1	68
5	 60	 70	1	75
6	 61	 71	2	72
7	 62	 72	1	58
8	 63	 73	1	66
9	 64	 74	1	74
10	 65	 75	6	32

II.D.3 EXPERIMENTAL

The details of the instruments used and of the chromatographic operations are the same as described in part I.A.3 of Chapter I. Carbon tetrachloride was distilled over P_2O_5 and stored over 4 A° molecular sieves. Acetonitrile was stored over $CaCl_2$ and finally distilled over P_2O_5. All the ketones used were purchased from commercial sources and used as received. NH_4-ZSM5 was purchased from P.V. Bakelites, The Netherlands and it was calcinated at 600°C for 8h to obtain H-ZSM5.

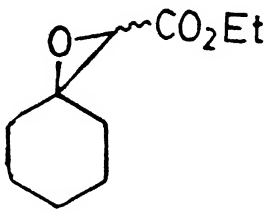
Procedure for Preparation of the Glycidic Ester[25] 64 :

In a two necked round bottom flask fitted with a dropping funnel, acetophenone (1.2 g, 10 mmol) was charged with freshly distilled ethylchloroacetate (1.25 g, 10.2 mmol). A solution of 394 mg of potassium in 8.5 ml of dry t-butanol was introduced into the dropping funnel and the system was evacuated and filled with argon. The t-butoxide was dropped in the reaction flask over a period of 1 hour with stirring, while the temperature was maintained at 15-25°C by cooling the flask in ice-box. After the addition was complete, the reaction mixture was stirred for additional 5 hours at room temperature. Most of the t-butanol was removed at reduced pressure and the residue was extracted with ether. The ether solution was washed with water followed by brine and finally dried over anhydrous sodium sulphate. After removal of ether on rotary evaporator, the crude product was purified by kugelrohr distillation or by column chromatography.

General Procedure for the Preparation of Glycidic Esters[6] :

To a suspension of sodium sand (253 mg, 11 g atom) in 3.5 ml of anhydrous xylene, was slowly added the mixture of a ketone (10 mmol) and ethylchloroacetate (1.25 g, 10.2 mmol) with stirring and cooling in an ice-salt bath. The reaction mixture was then allowed to come to room temperature during the period of one hour and stirred at that temperature for additional one hour (in the case of trans-1-decalone, it was heated at 60°C for 4 hours). The red coloured solution was then poured into 10 ml of ice-cold water and extracted with ether (3x25ml). The combined ether layer was washed with water (2x10 ml), brine (20 ml) and dried over anhydrous sodium sulphate. After the removal of ether on rotary evaporator xylene was removed under reduced pressure. The crude product so obtained was purified either by kugelrohr distillation or by column chromatography. Yields were tabulated in Table 1.

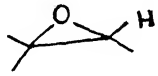
Ethyl-1-oxaspiro[2,5]-octan-2-carboxylate 56



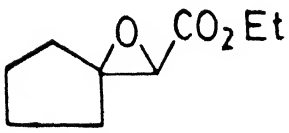
Yield : 54%

b.p : 100°C/2 mm Hg (literature b.p. : 90°C/1.5 mm Hg)

IR spectrum (neat) ν_{max}: 1750 and 1725 (CH_3CH_2-O-$\underset{\underset{O}{\|}}{C}$=O, glycidic) cm^{-1}

^1H NMR spectrum (CCl_4) : δ 4.2 (2H, q, -O$\underline{CH_2}CH_3$, J = 7 Hz), 3.1 (1H, s, ), 1.97-1.47 (10H, m, 5X-CH_2-) and 1.3 (3H, t -O$CH_2\underline{CH_3}$, J = 7 Hz).

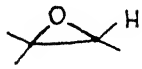
Ethyl-1-oxaspiro[2,4]-heptan-2-carboxylate 57



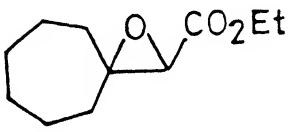
Yield : 37%

b.p. : 100°C/4 mm Hg (literature[6] b.p. : 72°C/1 mm Hg)

IR spectrum (neat) ν_{max} : 1745 (CH_3CH_2-O-C=O), 1725 (glycidic) cm^{-1}.

^1H NMR spectrum (CCl_4) : δ 4.2 (2H, q, $-OCH_2CH_3$, J = 7 Hz), 3.35 (1H, s, ), 2.1-1.43 (8H, m, 4X-CH_2-), 1.27 (3H, t, $-OCH_2CH_3$, J = 7 Hz).

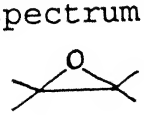
Ethyl-1-oxaspiro[2,6]-nonan-2-carboxylate 58



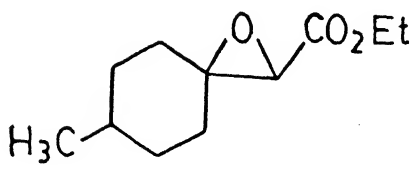
Yield : 40%

b.p : 105°C/1 mm Hg (literature[6] b.p. : 90°C/1 mm Hg)

IR specrum (neat) ν_{max} : 1750 and 1725 (CH_3CH_2-O-C=O, glycidic) cm^{-1}.

^1H NMR spectrum (CCl_4) : δ 4.17 (2H, q, $-OCH_2CH_3$, J = 7 Hz), 3.1 (1H, s, ), 2.0-1.47 (12H, m, 6X-CH_2-) and 1.3 (3H, t, $-OCH_2CH_3$, J = 7 Hz).

Ethyl-1-oxaspiro-[2,5]-octan-5-methyl-2-carboxylate 59



A clear liquid

Yield : 67%

b.p. : 115-170°C/10 mm

IR spectrum (neat) ν_{max} : 1750 and 1725 (CH_3CH_2-O-$\overset{O}{\overset{\|}{C}}$-, glycidic) cm^{-1}.

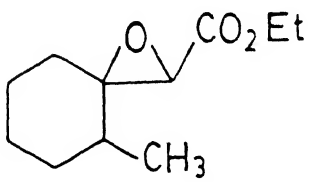
^1H NMR spectrum (CCl_4) : δ 0.95 (3H, d, $\rangle$CH-$\underline{C}H_3$), 1.2-2.1 (11H, m, methylenes, methines and methyl triplet of -O-$\overset{O}{\overset{\|}{C}}$-$CH_2$-$\underline{C}H_3$ at δ 1.3), 3.03-3.1 (1H, two s,), 4.2 (2H, q, -O-$C\underline{H}_2CH_3$, J = 7 Hz).

Mass spectrum m/z : 198 (M^+)

Anal. calcd. for $C_{11}H_{18}O_3$: C, 66.6; H, 9.04.

Found : C, 67.1; H, 9.38%

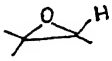
Ethyl-1-oxaspiro-[2,5]-octan-2-methyl-2-carboxylate 60



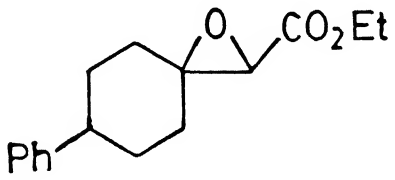
Yield : 38%

b.p. : 110°C/1 mm Hg

IR spectrum (neat) ν_{max} : 1750 and 1725 (CH_3CH_2-O-$\overset{|}{C}$=O-, glycidic) cm^{-1}.

^1H NMR spectrum (CCl_4) : δ 2.1-0.87 (15H, m, containing the -$OCH_2\underline{CH_3}$ triplet at δ 1.3 with J = 7 Hz and $\rangle$ CH-$\underline{CH_3}$ doublet at δ 0.95 with J = 6 Hz), 3.13 (1H, s, ), 4.2 (2H, q, -O-$\underline{CH_2}CH_3$, J = 7 Hz).

Ethyl-1-oxaspiro-[2,5]-octan-5-phenyl-2-carboxylate <u>61</u>



Viscous liquid

Yield : 56%

IR spectrum (neat) ν_{max} : 1750 and 1725 (CH_3CH_2-O-$\overset{|}{C}$=O, glycidic) cm^{-1}.

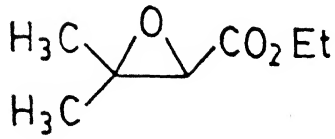
^1H NMR spectrum (CCl_4) : δ 1.3 (3H, t, -$OCH_2\underline{CH_3}$, J = 7 Hz), 1.65-2.15 (9H, m, methylenes and $\rangle$ $\underline{CH}$-Ph), 3.13-3.16 (1H, two s,), 4.2 (2H, q, -$OCH_2\underline{CH_3}$, J = 7 Hz) 7.0 (5H, s, aromatic).

Mass spectrum m/z : 260 (M^+)

Anal. Calcd. for $C_{16}H_{20}O_3$: C, 73.85; H, 7.69.

Found : C, 74.1; H, 8.31%.

:thyl-3-methyl-2,3-epoxy butanoate[26] 62

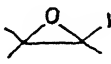


A clear liquid.

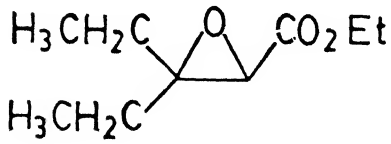
Yield : 55%

b.p. 90°C/30 mm Hg (Literature b.p. : 163-168°C)

IR spectrum (neat) ν_{max} : 1755 and 1730 (CH_3CH_2-O-C=O, glycidic) cm^{-1}.

^1H NMR spectrum (CCl_4) : δ 1.15 (3H, t, $-OCH_2CH_3$), 1.30-1.36 (6H, s, >C-$(CH_3)_2$), 3.09 (1H, s, ), 4.12 (2H, q, $-OCH_2CH_3$, J = 7 Hz).

Ethyl-3-ethyl-2,3-epoxy pentanoate 63

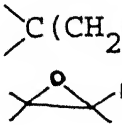


A colourless liquid

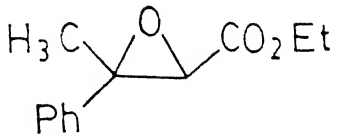
Yield : 55%

b.p. : 112°C/25 mm Hg (Literature b.p. : 109-110°C/25 mm Hg)

IR spectrum (Neat) ν_{max} : 1753 and 1730 (CH_3CH_2-O-C=O, glycidic) cm^{-1}.

^1H NMR (CCl_4) : δ 0.85 (3H, t, $-OCH_2CH_3$), 1.34 and 1.29 (6H, two t, >C$(CH_2CH_3)_2$), 1.59 and 1.48 (4H, two q, >C$(CH_2CH_3)_2$), 3.15 (1H, s, ), 4.15 (2H, q, $-OCH_2CH_3$, J = 7 Hz).

Ethyl-3-phenyl-2,3-epoxy butanoate[26] **64**

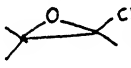
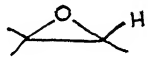


A light yellow coloured oil.

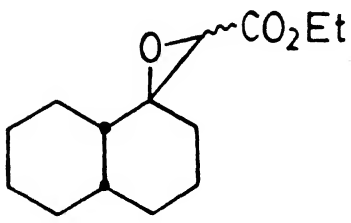
Yield : 70%

b.p. : 105°C/5 mm Hg (Literature b.p. : 111-114°C/3 mm Hg)

IR spectrum (neat) ν_{max} : 1750 and 1730 (CH_3CH_2-O-$\overset{\overset{O}{\|}}{C}$=O, glycidic) cm^{-1}.

^1H NMR spectrum (CCl_4) : δ 1.29 and 0.86 (6H, two t, -O-CH_2CH_3, J = 7 Hz and J = 6.5 Hz respectively (relative areas ca 1:1), 1.66 and 1.41 (3H, two s, ), 3.45 and 3.24 (1H,  , J = 6 Hz), 4.25 and 3.69 (2H, two q, -O$\underline{CH_2}CH_3$, J = 7 Hz and J = 6.5 Hz respectively (relative areas ca 1:1)), 7.15 (5H, s, aromatic).

Glycidic ester 65



Yield : 46%

IR spectrum (neat) ν_{max} : 1750 and 1725 (CH_3CH_2-O-$\overset{\overset{O}{\|}}{C}$=O, glycidic) cm^{-1}.

^1H NMR spectrum (CCl_4) : δ 4.2 (2H, q, -O$\underline{CH_2}CH_3$, J = 7 Hz), 3.45 (1H, s,), 2.1-1.0 (19H, m, containing the -O$CH_2\underline{CH_3}$

triplet, J = 7 Hz).

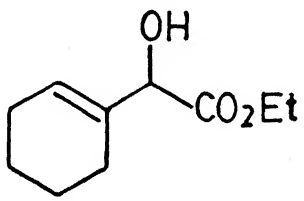
Mass spectrum : m/z 238 (M^+)

Anal. Calcd. for $C_{14}H_{22}O_3$: C, 70.55; H, 9.31. Found : C, 70.41; H, 9.21%

General procedure for the isomerisation of glycidic esters with H-ZSM-5

A glycidic ester (0.5 mmol) was taken in dry benzene (4 ml) in a round bottom flask. To this solution was added weight equivalent H-ZSM-5 zeolite and refluxed for the time mentioned in Table 1. The reaction mixture was filtered through a pad of celite and the pad was washed thoroughly with dichloromethane. Evaporation of the solvent at the rotary evaporator followed by purification of the crude product by column chromatography (SiO_2). [Eluent : Petroleum ether - Ethyl acetate] gave the pure α-hydroxy- β,γ-unsaturated ester.

Ethyl-2-hydroxy-2-(1-cyclohexenyl) acetate 66



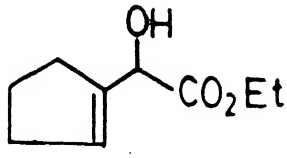
Yield : 74%

IR spectrum (neat) ν_{max} : 3480 (br, -OH), 1730 (C=O) cm^{-1}.

^1H NMR spectrum (CCl_4) : δ 1.3 (3H, t, $-OCH_2\underline{CH_3}$, J = 7 Hz), 1.5-1.9 (4H, m, $2X-CH_2-$), 1.97-2.4 (4H, m, allylic CH_2's), 3.1 (1H, br, s, -OH, exchangeable with D_2O), 4.1-4.6 (3H, m, $>\underline{CH}OH$,

containing the $-C\underline{H}_2CH_3$ quartet, J = 7 Hz), 5.83 (1H, br s, =CH-). Mass spectrum m/z [rel. int.] : 184 [5, M^+], 111 [100, (M^+ - CO_2Et)], 83 [28].

Ethyl-2-hydroxy-2-(1-cyclopentenyl) acetate 67



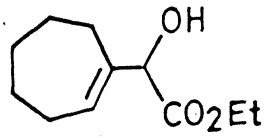
Yield : 73%

IR spectrum (neat) ν_{max} : 3460 (br, -OH), 1730 (C=O) cm^{-1}.

^1H NMR spectrum (CCl_4) : δ 1.3 (3H, t, $-OCH_2\underline{CH}_3$, J = 7 Hz), 1.67-2.1 (2H, m, $-CH_2-$), 2.2-2.7 (4H, m, allylic CH_2's), 3.05 (1H, br s, -OH, exchangeable with D_2O), 4.25 (2H, q, $-O\underline{CH}_2CH_3$, J = 7 Hz), 4.7 (1H, br s, $\rangle C\underline{H}OH$), 5.77 (1H, br s, =CH-).

Mass spectrum m/z [rel. int.] : 170 [10, M^+], 97 [100, (M^+-CO_2Et)].

Ethyl-2-hydroxy-2-(1-cycloheptenyl) acetate 68



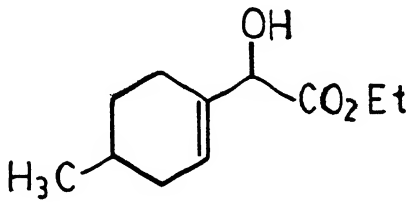
Yield : 81%

IR spectrum (neat) ν_{max} : 3500 (br s, -OH), 1730 (C=O) cm^{-1}.

^{1}H NMR spectrum (CCl_4) : δ 1.17-1.9 (9H, m, 3X-CH_2-, containing the -$OCH_2\underline{C}H_3$ triplet, J = 7 Hz), 1.97-2.45 (4H, m, allylic CH_2's), 2.97 (1H, br, s, -OH), 4.05-4.5 (3H, m, >$C\underline{H}OH$, containing the -$OC\underline{H}_2CH_3$ quartet, J = 7 Hz), 5.93 (1H, t, =CH-, J = 6 Hz).

Mass spectrum m/z [re. int.] : 198 [6, M^+], 125 [100, (M^+-CO_2Et)].

Ethyl-2-hydroxy-2-(4-methyl-1-cyclohexenyl) acetate 69



Thick liquid

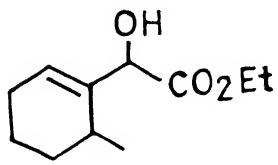
Yield : 68%

IR spectrum (neat) ν_{max} : 1780 (br, -OH), 1720 (C=O) cm^{-1}.

^{1}H NMR spectrum (CCl_4) : δ 0.97 (3H, d, -$\underline{C}H\underline{C}H_3$, J = 3 Hz), 1.27 (3H, t, -$OCH_2\underline{C}H_3$, J = 7 Hz), 1.53-2.5 (7H, m, methylenes and -$\underline{C}H\underline{C}H_3$), 2.8 (1H, br s, -OH), 3.75-4.15 (3H, m, -$\underline{C}H\underline{O}H$ and the -$OC\underline{H}_2CH_3$ quartet, J = 7 Hz), 5.6 (1H, br s =CH-).

Mass spectrum m/a : 198 (M^+), 125 (M^+-CO_2Et).

α-Hydroxy-β,ν-unsaturated-ester 70



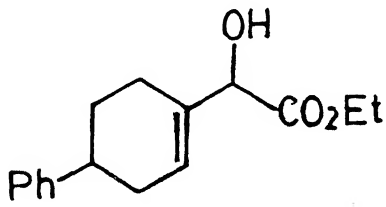
Yield : 75%

IR spectrum (neat) ν_{max} : 3480 (br, -OH), 1730 (C=O) cm^{-1}.

^1H NMR (CCl_4) : δ 0.97 (3H, d, >CH-$\underline{CH}_3$, J = 6 Hz), 1.27 (3H, t, -$OCH_2\underline{CH}_3$, J = 7 Hz), 1.53-2.0 (4H, m, 2X-CH_2-), 2.0-2.5 (3H, m, allylic >CH- and -CH_2-), 2.85 (1H, br s, -OH), 4.1-4.6 (3H, m, >$\underline{CH}$OH, containing the -$O\underline{CH}_2CH_3$ quartet, J = 7 Hz), 5.73 (1H, br s, =CH-).

Mass spectrum m/z [rel. int.] : 198 [5, M^+], 125 [100, (M^+-CO_2Et)], 97 [30].

Ethyl-[2-hydroxy-2-(4-phenyl-1-cyclohexenyl)] acetate 71



White crystalline solid

Yield : 72%

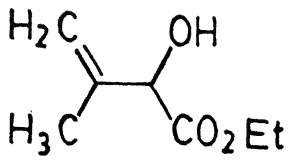
m.p. : 58°C [solvent of crystallisation : ethanol]

IR spectrum (KBr) ν_{max} : 3440 (br, -OH) and 1720 (C=O) cm^{-1}.

^1H NMR spectrum (CCl_4) δ 1.3 (3H, t, -$OCH_2\underline{CH}_3$, J = 7 Hz), 1.5-2.2 (7H, m, 3X-CH_2- and >$\underline{CH}$Ph), 3.1 (1H, br s, -OH), 3.73-4.46 (3H, m, >$\underline{CH}$OH and the -$O\underline{CH}_2CH_3$ quartet, J = 7 Hz), 5.75 (1H, br s, =CH-), 7.1 (5H, s, aromatic).

Mass spectrum m/z : 261 $(M+1)^+$, 188 [$(M+1)^+$-CO_2Et)]

Ethyl-2-hydroxy-3-methyl-3-butenoate 72



Colourless liquid

Yield : 58%

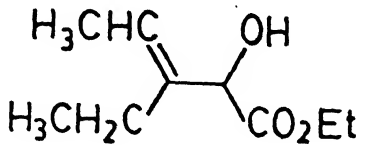
b.p. : 70°C/10 mm (Lit.[27] : 68-69°C/10 mm)

IR spectrum (neat) ν_{max} : 3460 (-OH), 1730 (C=O) cm^{-1}.

^1H NMR (CCl_4) : δ 1.29 (3H, t, $-OCH_2-\underline{CH_3}$), 1.63 (3H, m, $=C(\underline{CH_3})-$), 3.18 (1H, br s, -OH), 4.13 (2H, q, $-O\underline{CH_2}CH_3$, J = 7 Hz), 4.5 (1H, s, $>\underline{CH}OH$), 4.7-5.2 (3H, m, =CH-)

Mass spectrum m/z : 145 $(M+1)^+$, 71 (M^+-CO_2Et)

Ethyl-3-ethyl-2-hydroxy-3-pentenoate 73



Free mobile liquid

Yield : 66%

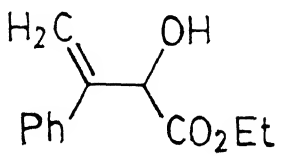
b.p. : 83°C/6 mm (Lit.[6] 80-81°C/5 mm)

IR spectrum (neat) ν_{max} : 3500 (-OH), 1715 (C=O) cm^{-1}

^1H NMR spectrum (CCl_4) : δ 0.90 (3H, t, $-OCH_2\underline{CH_3}$, J = 7 Hz), 1.20 (3H, t, $\underline{CH_3}CH_2C{=}CH-$, J = 7 Hz), 1.53 and 1.59 (3H, two d, relative areas ca 2:1, $CH_3\overset{|}{C}{=}$), 1.92 (2H, t, $CH_3\underline{CH_2}$ C=CH-, J = 7 Hz), 3.3 (1H, br d, -OH), 4.03 (2H, q, $-O\underline{CH_2}CH_3$, J = 7 Hz), 4.28 and 4.82 (1H, two br s, relative area ca 2:1, $>\underline{CH}OH$)

Mass spectrum m/z : 171 (M^+), 98 (M^+-CO_2Et)

Ethyl-2-hydroxy-3-phenyl-3-butenoate 74



Colourless thick oil

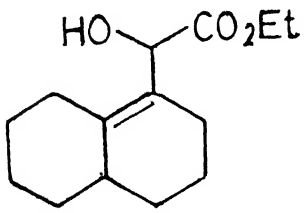
Yield : 74%

IR spectrum (neat) ν_{max} : 3500 (-OH), 1720 (C=O) cm^{-1}.

^1H NMR spectrum (CCl_4) : δ 1.01 (3H, t, $-OCH_2\underline{CH_3}$), 3.0 (1H, br s, -OH), 3.95 (2H, q, $-O\underline{CH_2}CH_3$), 4.69 (1H, br s, >C<u>H</u>OH), 5.15 (2H, s, =CH-), 7.03 (5H, s, aromatic)

Mass spectrum m/z : 206 (M^+), 133 (M^+-CO_2Et)

α-Hydroxy-β,ν-unsaturated ester 75



Yield : 32%

IR spectrum (neat) ν_{max} : 3500 (br, -OH), 1730 (C=O) cm^{-1}

^1H NMR spectrum (CCl_4) : δ 1.2-2.5 (18H, m, >CH-, $7X-CH_2-$, containing the $-OCH_2\underline{CH_3}$ triplet, J = 7 Hz), 2.83 (1H, br s, -OH), 4.1-4.6 (3H, m, >C<u>H</u>OH, containing the $-O\underline{CH_2}CH_3$ quartet, J = 7 Hz)

Mass spectrum m/z [rel. int.] : 238 [5, M^+]m 165 [100, (M^+-CO_2Et).

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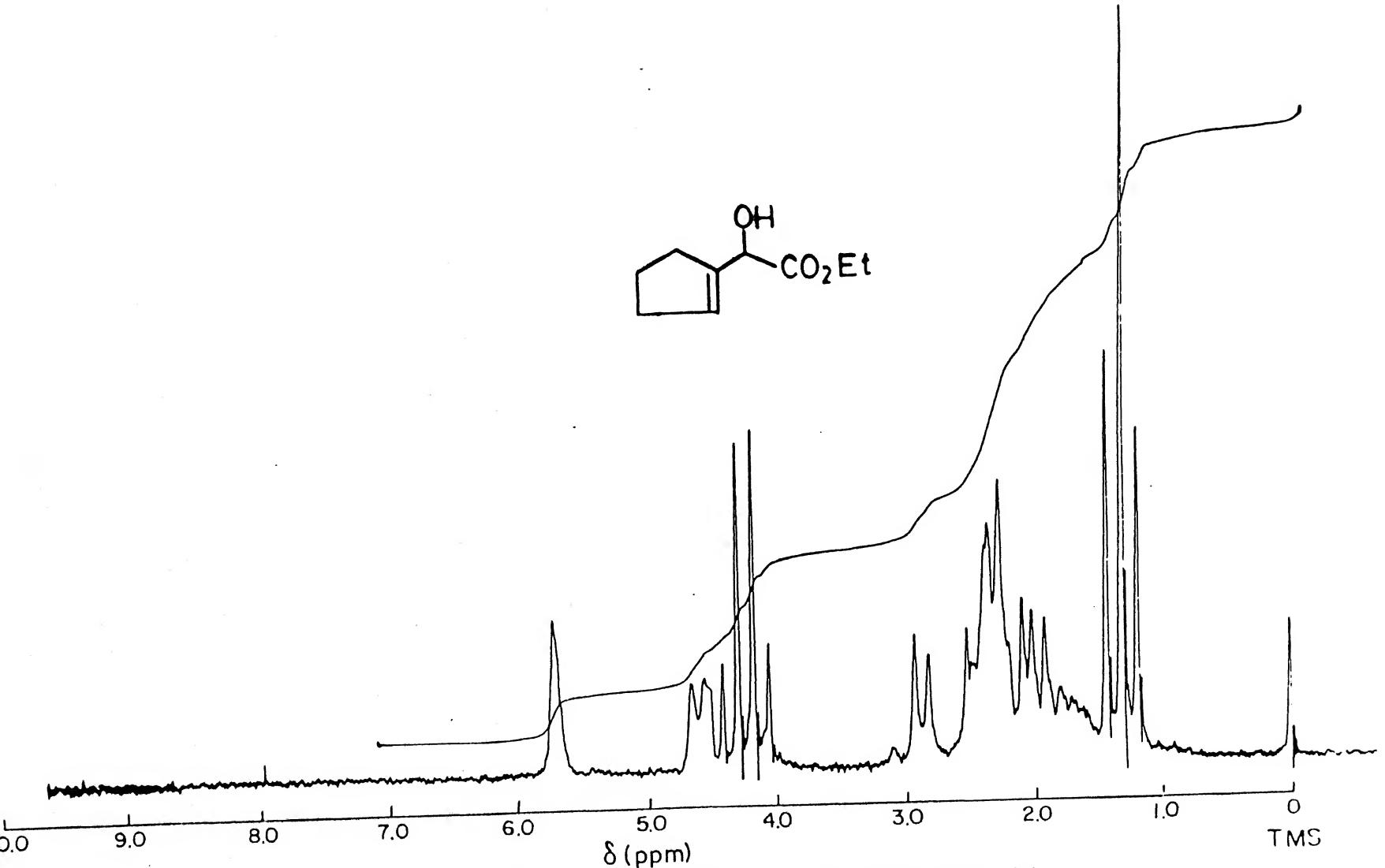
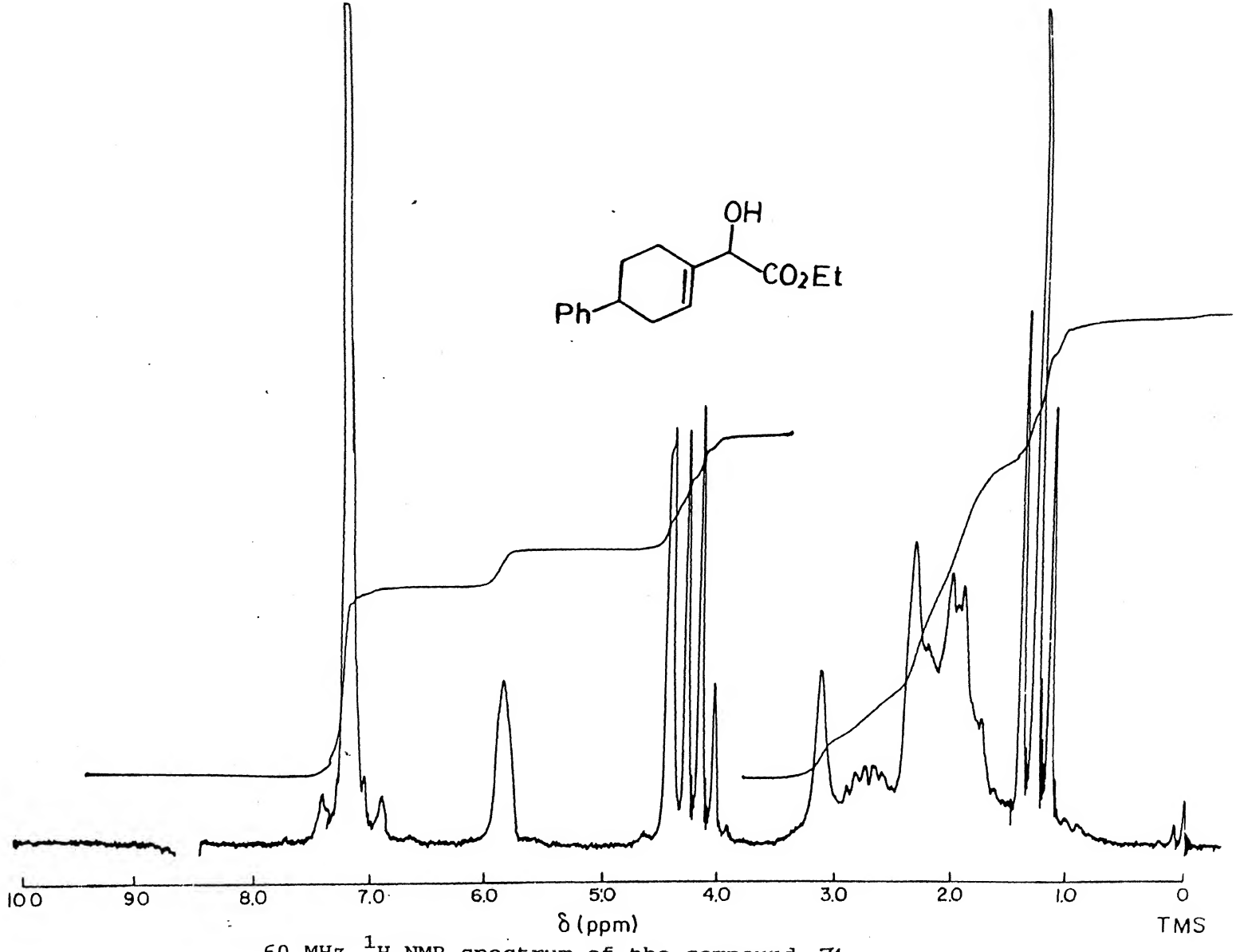
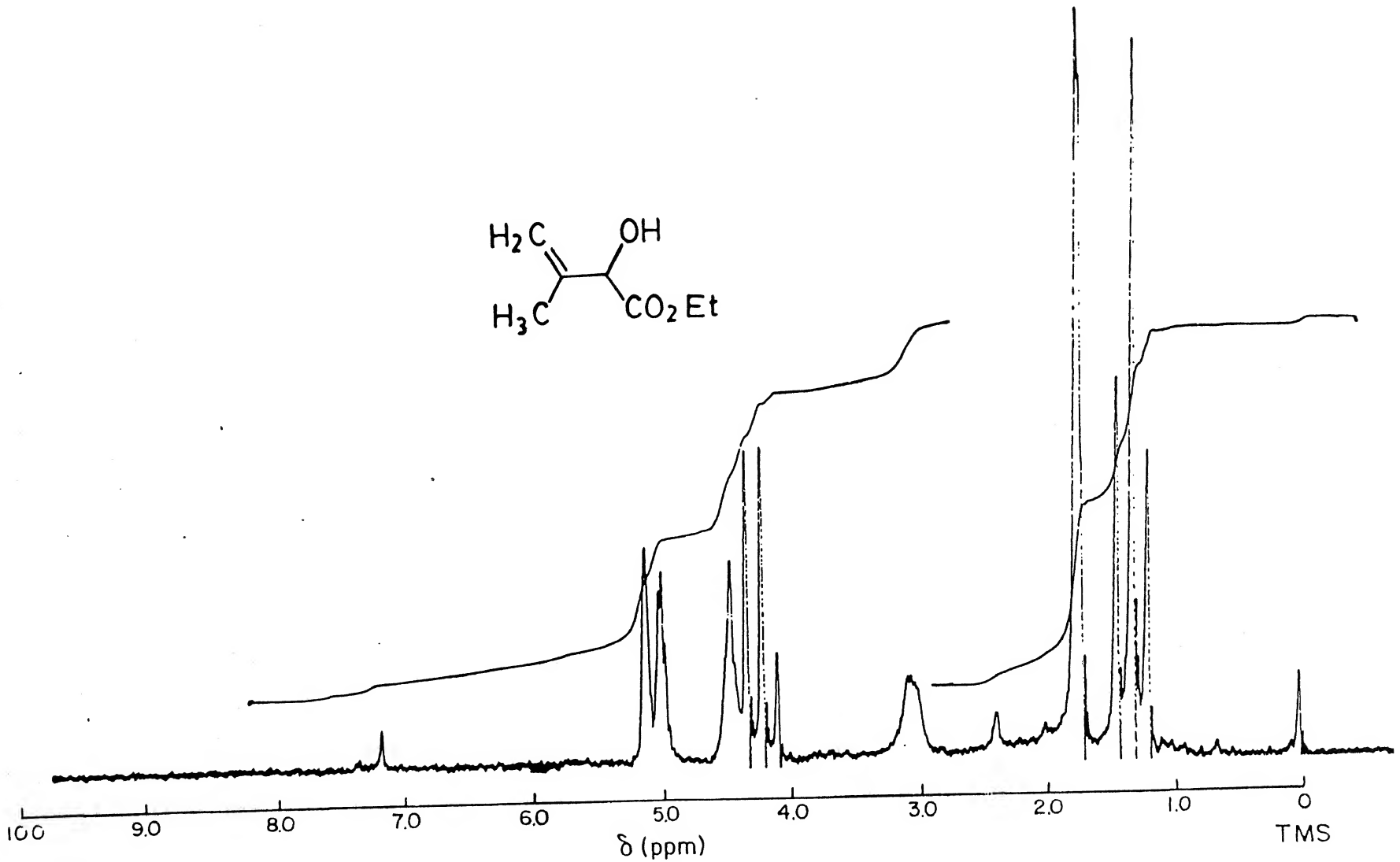


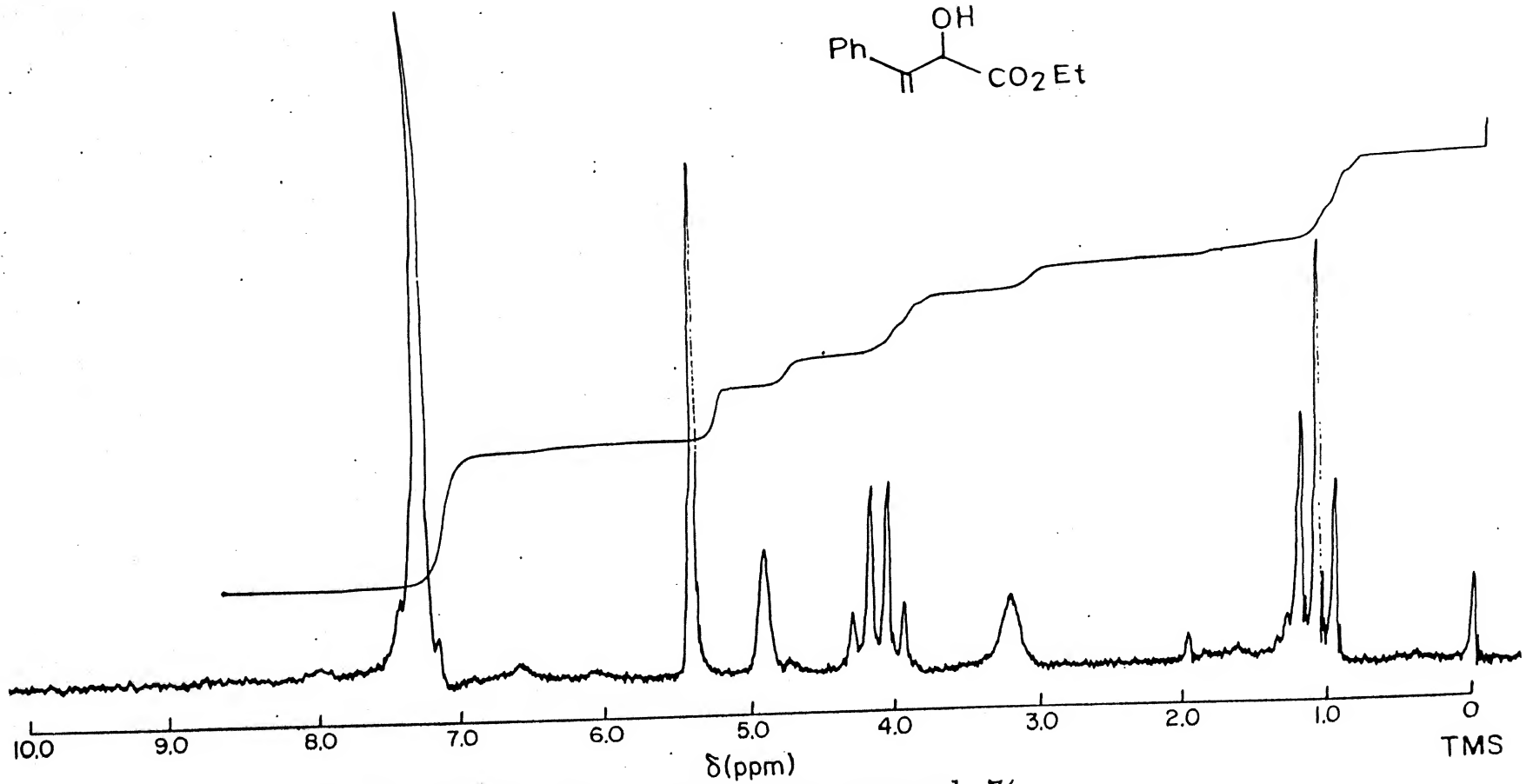
60 MHz ^{1}H NMR spectrum of the compound 67



60 MHz ^{1}H NMR spectrum of the compound 71



60 MHz ^{1}H NMR spectrum of the compound 72



60 MHz ^{1}H NMR spectrum of the compound 74